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(12) **United States Patent**
Cai et al.(10) **Patent No.:** **US 9,199,983 B2**
(45) **Date of Patent:** **Dec. 1, 2015**(54) **3-ARYL-6-ARYL-[1,2,4]TRIAZOLO[4,3- α]
PYRIDINES AS INHIBITORS OF CELL
PROLIFERATION AND THE USE THEREOF**USPC 546/119, 121; 514/303
See application file for complete search history.(76) Inventors: **Suixiong Cai**, Jiangsu (CN); **Ye Edward Tian**, Jiangsu (CN); **Haijun Dong**, Shanghai (CN); **Lei Chen**, Jiangsu (CN); **Zenghui Yu**, Jiangsu (CN); **Feng Yin**, Jiangsu (CN); **Sheng Bi**, Jiangsu (CN); **Lijun Liu**, Jiangsu (CN); **Lizhen Wu**, Jiangsu (CN)(56) **References Cited**

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(2), (4) Date: **Jul. 10, 2013**(87) PCT Pub. No.: **WO2012/065546**PCT Pub. Date: **May 24, 2012**(65) **Prior Publication Data**

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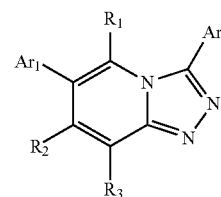
(51) **Int. Cl.****C07D 401/14** (2006.01)
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C07D 471/04 (2006.01)
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A61K 31/506 (2006.01)
A61K 45/06 (2006.01)
A61N 5/10 (2006.01)(52) **U.S. Cl.**CPC **C07D 471/04** (2013.01); **A61K 31/437** (2013.01); **A61K 31/444** (2013.01); **A61K 31/506** (2013.01); **A61K 45/06** (2013.01); **A61N 5/10** (2013.01)(58) **Field of Classification Search**

CPC C07D 401/14; A61K 31/437

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Primary Examiner — Niloofar Rahmani(74) *Attorney, Agent, or Firm* — Sterne, Kessler, Goldstein & Fox P.L.L.C.(57) **ABSTRACT**Disclosed are 3-aryl-6-aryl-[1,2,4]triazolo[4,3-a]pyridines thereof, represented by the Formula (I) wherein Ar₁, Ar₂, R₁-R₃ are defined herein. Compounds having Formula (I) are inhibitors of cell proliferation. Therefore, compounds of the invention may be used to treat clinical conditions in which uncontrolled growth and spread of abnormal cells occurs.

(I)

19 Claims, No Drawings

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3-ARYL-6-ARYL-[1,2,4]TRIAZOLO[4,3- α]PYRIDINES AS INHIBITORS OF CELL PROLIFERATION AND THE USE THEREOF

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention is in the field of medicinal chemistry. In particular, the invention relates to 3-aryl-6-aryl-[1,2,4]triazolo[4,3- α]pyridines, and the use of these compounds as therapeutically effective anticancer agents.

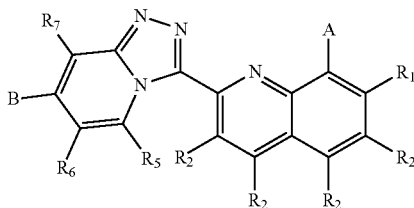
2. Related Art

One of the hallmarks of cancer is the uncontrolled cell proliferation. Therefore, the discovery and development of antiproliferative agents which are cytotoxic to cancer cells and inhibit cancer cell growth can lead to effective treatment for cancer. Many novel chemotherapeutic agents have been discovered and developed in the past 50 years, including paclitaxel and docetaxel, doxorubicin and epirubicin, topotecan and irinotecan, cisplatin and carboplatin, as well as vincristine and vinblastine, and these cytotoxic drugs have been widely used for the treatment of both leukemia and solid tumors. More recently, significant successes have been made with targeted therapies, such as the successful development of BCR-ABL tyrosine kinase inhibitor imatinib for the treatment of chronic myeloid leukemia. However, cancer is a complex, aggressive and lethal disease. It remains a great challenge to find more effective anticancer drugs.

The mechanism of action of many current anticancer drugs frequently involves an attack at specific phases of the cell cycle to cause cell cycle arrest. In brief, the cell cycle refers to the stages through which cells progress during their lifetime. Normally, cells exist in a resting phase termed G₀. During multiplication, cells progress to a stage in which DNA synthesis occurs, termed S. Later, cell division, or mitosis occurs, in a phase called M. Antineoplastic drugs, such as vincristine, vinblastine, and paclitaxel are M phase specific.

It has been known that many cancer chemotherapeutic drugs can trigger cancer cells to undergo apoptosis. The mechanism of apoptosis involves a cascade of initiator and effector caspases that are activated sequentially. Caspases are a family of cysteine proteases that require aspartic acid residues at the P₁ position of substrates for cleavage. Among these caspases, caspase-3, 6, and 7 are key effector caspases that cleave multiple protein substrates in cells, leading irreversibly to cell death. Cellular caspase activity can be measured using caspase substrates.

WO2010022076 disclosed the following triazolopyridine derivatives for use as PIM kinase inhibitors, wherein A=OR₁₀ or NR₁₁R₁₂; B=H, F, Cl, OH, etc; R₆=H, F, Br, Me, CN, Ph, etc.



SUMMARY OF THE INVENTION

The invention provides novel 3-aryl-6-aryl-[1,2,4]triazolo[4,3- α]pyridines, as represented in Formulae I and II. These compounds have antiproliferative activities.

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The present invention also provides pharmaceutical compositions comprising a compound of Formula I or II in an effective amount to treat or ameliorate diseases caused by uncontrolled cell proliferation in a mammal.

The invention also relates to the use of the compounds of Formula I or II for treating, preventing or ameliorating diseases caused by uncontrolled cell proliferation in a mammal, in particular, neoplasia and cancer.

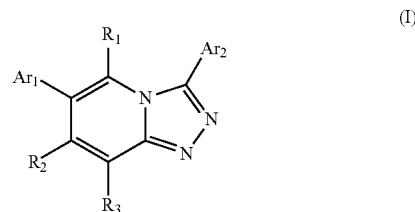
The invention also provides a pharmaceutical composition useful for treating disorders responsive to these antiproliferative agents, containing an effective amount of a compound of one of the Formula I or II in admixture with one or more pharmaceutically acceptable carriers or diluents.

The invention also is directed to methods for the preparation of novel compounds of Formulae I and II.

DETAILED DESCRIPTION OF THE INVENTION

The inhibitors of cell proliferation of the present invention include 3-aryl-6-aryl-[1,2,4]triazolo[4,3- α]pyridines, as represented in Formulae I and II. Therefore, compounds of Formulae I and II are useful for treating disorders responsive to antiproliferative agents.

Specifically, compounds of the present invention are represented by Formula I:



or pharmaceutically acceptable salts or prodrugs thereof, wherein:

Ar₁ and Ar₂ independently are an optionally substituted aryl or an optionally substituted heteroaryl;

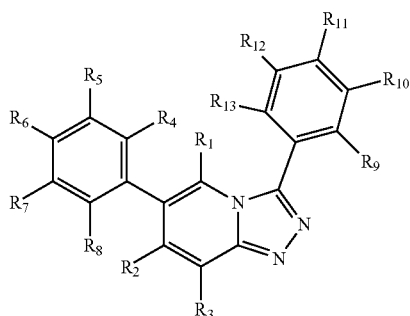
R₁-R₃ independently are hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted C₁₋₁₀ alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, acyloxy, azido, carboxy, carbonylamido or optionally substituted alkylthiol;

with the proviso that Ar₂ is not 8-substituted-quinolin-2-yl when Ar₁ is phenyl.

Preferred compounds of Formula I include compounds wherein Ar₁ and Ar₂ are phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, isoxazolyl, pyrazolyl, imidazolyl, thienyl, furyl or pyrrolyl, each of which is optionally substituted. More preferably, Ar₁ and Ar₂ are phenyl or pyridyl. Another group of preferred compounds of Formula I include compounds wherein R₁, R₂ and R₃ are hydrogen.

One group of preferred compounds of the present invention are represented by Formula II:

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or pharmaceutically acceptable salts or prodrugs thereof, wherein:

R_1 - R_3 independently are hydrogen, halo, optionally substituted amino, optionally substituted alkoxy, optionally substituted C_{1-10} alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, acyloxy, azido, carboxy, carbonylamido or optionally substituted alkylthiol;

R_4 - R_{13} independently are hydrogen, halo, amino, alkoxy, C_{1-10} alkyl, haloalkyl, aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, hydroxyalkoxy, aminoalkyl, aminoalkoxy, carboxyalkyl, nitro, cyano, acylamido, hydroxy, thiol, acyloxy, azido, carboxy, carbonylamido, alkylsulfonyl, aminosulfonyl, dialkylaminosulfonyl, alkylsulfinyl, or alkylthiol; or

R_4 and R_5 , or R_5 and R_6 , or R_6 and R_7 , or R_7 and R_8 , or R_8 and R_9 , or R_9 and R_{10} , or R_{10} and R_{11} , or R_{11} and R_{12} , or R_{12} and R_{13} , taken together with the atoms to which they are attached to form an aryl, heteroaryl, partially saturated carbocyclic or partially saturated heterocyclic group, wherein said group is optionally substituted.

One group of preferred compounds of Formula II include compounds wherein R_4 and R_5 , or R_5 and R_6 , or R_6 and R_7 , or R_7 and R_8 , or R_8 and R_9 , or R_9 and R_{10} , or R_{10} and R_{11} , or R_{11} and R_{12} , or R_{12} and R_{13} are taken together to form a structure selected from the group consisting of $-\text{OCH}_2\text{O}-$, $-(\text{CH}_2)_3-$, $-(\text{CH}_2)_4-$, $-\text{OCH}_2\text{CH}_2\text{O}-$, $-\text{CH}_2\text{N}(\text{R}_{14})\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{N}(\text{R}_{14})\text{CH}_2-$, $-\text{CH}_2\text{N}(\text{R}_{14})\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{N}(\text{R}_{14})\text{CH}_2\text{CH}_2-$, $-\text{N}(\text{R}_{14})-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{N}(\text{R}_{14})-$, $-\text{N}(\text{R}_{14})-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{R}_{14})-$, $-\text{N}(\text{R}_{14})-\text{CH}=\text{N}-$, $-\text{N}=\text{CH}-\text{N}(\text{R}_{14})-$, $-\text{O}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{O}-$, $-\text{S}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{S}-$, $-\text{N}-\text{C}(=\text{O})-\text{O}-$, $-\text{N}-\text{CH}_2-\text{CH}_2-\text{N}-$ and $-\text{N}=\text{CH}-\text{CH}=\text{N}-$, wherein R_{14} is hydrogen, C_{1-10} -alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl or aminoalkyl.

Exemplary preferred compounds of Formulae I and II include, without limitation:

- 3-(2-Methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3-(2-Methoxyphenyl)-6-(3-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3,6-Bis(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(2-Fluoro-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(4-Methoxy-3-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

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(II)

- 6-(4-Ethylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(4-Methoxy-2-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(4-Benzoyloxy-3-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3-(2-Methoxyphenyl)-6-(4-methyl-3-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3-(2-Methoxyphenyl)-6-(4-trifluoromethoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(3-Hydroxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(4-Hydroxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(Benzo[d][1,3]dioxol-5-yl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3-(2-Methoxyphenyl)-6-(6-methoxypyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(4-Ethoxy-3-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(4-Dimethylaminophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3-(2-Methoxyphenyl)-6-(2-methoxypyrimidin-5-yl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(3-Chloro-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(3-Hydroxy-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(3-Methoxy-4-nitrophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3-(2-Methoxyphenyl)-6-(4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3-(2-Methoxyphenyl)-6-(3-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3-(2-Methoxyphenyl)-6-phenyl-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(2,4-Dimethylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3-(3-Chloro-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3-(2-Methoxyphenyl)-6-(4-trifluoromethylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(3-Methoxy-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3-(2-Methoxyphenyl)-6-(3,4,5-trimethoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(3,5-Dimethyl-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(3,4-Dimethoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(3,4-Dimethylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(3-Fluoro-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(4-Hexyloxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(3-Fluoro-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(2,4-Dimethoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(4-Benzoyloxy-3-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 6-(4-Ethoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
- 3-(2-Methoxyphenyl)-6-(4-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyridine;

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6-(4-Methoxy-3-nitrophenyl)-3-(2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Hydroxy-3-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Methoxy-3-nitrophenyl)-3-(2-methoxy-5-nitrophenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Amino-3-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(3-Amino-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(3-Aminophenyl)-3-(2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine hydrochloride;
 6-(3-Amino-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine hydrochloride;
 6-(4-Aminophenyl)-3-(2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine hydrochloride;
 6-(4-Methylaminophenyl)-3-(2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine hydrochloride;
 3-(4-Chloro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(3-Amino-4-methoxyphenyl)-3-(4-chloro-2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(3-Hydroxy-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(3-Amino-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(3-Fluoro-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(2-Methoxyphenyl)-6-(4-methoxyphenyl)-7-methyl-[1,2,4] triazolo[4,3-a]pyridine;
 3-(2-Methoxyphenyl)-6-(4-methoxyphenyl)-8-methyl-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Hydroxy-3-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(4-Chloro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(4-Fluoro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(4-Bromo-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(2-Methoxy-4-trifluoromethylphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(2,6-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(2,5-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(6-Fluoro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3,6-Bis(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(3-Bromo-2,6-dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(2-Methoxy-4-methylphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-(2-trifluoromethoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-phenyl-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-(2,4,5-trimethoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(2-Methoxy-4-nitrophenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(2,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-(2,3,4-trimethoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(2,3-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;

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3-(2-Ethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-(2-methoxy-5-sulfamoylphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(2-Methoxy-5-methylphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(3-Methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-(2-methylphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-(2-methylaminophenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(2-Dimethylaminophenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(3-Amino-4-methoxyphenyl)-3-(4-chloro-2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine hydrochloride;
 6-(3-Amino-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4] triazolo[4,3-a]pyridine hydrochloride;
 3-(4-Chloro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine hydrochloride;
 3-(2-Methoxy-4-methylphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine hydrochloride;
 3-(2-Chloropyridin-3-yl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-(2-methoxypyridin-3-yl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(4-Amino-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine hydrochloride;
 3-(4-Chloro-2-methoxyphenyl)-6-(4-methylaminophenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 3-(4-Chloro-2-methoxyphenyl)-6-(3-hydroxy-4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(3-Amino-4-methylphenyl)-3-(4-chloro-2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(3-Amino-4-methylphenyl)-3-(4-methyl-2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;
 6-(4-Methylaminophenyl)-3-(4-methyl-2-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine;

and pharmaceutically acceptable salts or prodrugs thereof.
 The term "alkyl" as employed herein by itself or as part of another group refers to both straight and branched chain radicals of up to ten carbons. Useful alkyl groups include straight-chained and branched C₁₋₁₀ alkyl groups, more preferably C₁₋₆ alkyl groups. Typical C₁₋₁₀ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, 3-pentyl, hexyl and octyl groups, which may be optionally substituted.

The term "amino" as employed herein by itself or as part of another group is primary (—NH₂), secondary (—NHR), or tertiary (—NRR), wherein R is independently an optionally substituted alkyl, aryl, heteroaryl, or two R groups together with the nitrogen form a 5 or 6 membered heterocyclic group, optionally containing an additional N or O atom.

The term "alkenyl" as employed herein by itself or as part of another group means a straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including at least one double bond between two of the carbon atoms in the chain. Typical alkenyl groups include ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl and 2-butenyl.

The term "alkynyl" is used herein to mean a straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, wherein there is at least one triple bond between two of the carbon atoms in the chain. Typical alkynyl groups include ethynyl, 1-propynyl, 1-methyl-2-propynyl, 2-propynyl, 1-butyne and 2-butyne.

Useful alkoxy groups include oxygen substituted by one of the C₁₋₁₀ alkyl groups mentioned above, which may be optionally substituted. Alkoxy substituents include, without limitation, halo, morpholino, and amino including alkylamino and dialkylamino, and carboxy including esters thereof.

Useful alkylthio groups include sulfur substituted by one of the C₁₋₁₀ alkyl groups mentioned above, which may be optionally substituted. Also included are the sulfoxides and sulfones of such alkylthio groups.

Useful amino and optionally substituted amino groups include —NH₂, —NHR₁₅ and —NR₁₅R₁₆, wherein R₁₅ and R₁₆ are C₁₋₁₀ alkyl or cycloalkyl groups, or R₁₅ and R₁₆ are combined with the N to form a ring structure, such as a piperidine, or R₁₅ and R₁₆ are combined with the N and other group to form a ring, such as a piperazine. The alkyl group may be optionally substituted.

Optional substituents on the alkyl, alkoxy, alkylthio, alkynyl, alkynyl, cycloalkyl, carbocyclic and heterocyclic groups include one or more halo, hydroxy, carboxyl, amino, nitro, cyano, C₁₋₆ acylamino, C₁₋₆ acyloxy, C₁₋₆ alkoxy, aryloxy, alkylthio, C₆₋₁₀ aryl, C₄₋₇ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl(C₂₋₆)alkenyl, C₆₋₁₀ aryl(C₂₋₆)alkynyl, saturated and unsaturated heterocyclic or heteroaryl.

Optional substituents on the aryl, arylalkyl, arylalkenyl, arylalkynyl and heteroaryl and heteroarylalkyl groups include one or more halo, methylenedioxy, C₁₋₆ haloalkyl, C₆₋₁₀ aryl, C₄₋₇ cycloalkyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl(C₁₋₆)alkyl, C₆₋₁₀ aryl(C₂₋₆)alkenyl, C₆₋₁₀ aryl(C₂₋₆)alkynyl, C₁₋₆ hydroxyalkyl, nitro, amino, ureido, cyano, C₁₋₆ acylamino, hydroxy, thiol, C₁₋₆ acyloxy, azido, C₁₋₆ alkoxy, carboxy, di(C₁₋₁₀-alkyl) amino, alkylsulfonfyl, aminosulfonfyl, dialkylaminosulfonfyl, or alkylsulfonfyl.

The term “aryl” as employed herein by itself or as part of another group refers to monocyclic, bicyclic or tricyclic aromatic groups containing from 6 to 14 carbons in the ring portion.

Useful aryl groups include C₆₋₁₄ aryl, preferably C₆₋₁₀ aryl. Typical C₆₋₁₄ aryl groups include phenyl, naphthyl, phenanthrenyl, anthracenyl, indenyl, azulenyl, biphenyl, biphenylene and fluorenyl groups.

The term “carbocycle” as employed herein include cycloalkyl and partially saturated carbocyclic groups. Useful cycloalkyl groups are C₃₋₈ cycloalkyl. Typical cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Useful saturated or partially saturated carbocyclic groups are cycloalkyl groups as described above, as well as cycloalkenyl groups, such as cyclopentenyl, cycloheptenyl and cyclooctenyl.

Useful halo or halogen groups include fluorine, chlorine, bromine and iodine.

The term “arylalkyl” is used herein to mean any of the above-mentioned C₁₋₁₀ alkyl groups substituted by any of the above-mentioned C₆₋₁₄ aryl groups. Preferably the arylalkyl group is benzyl, phenethyl or naphthylmethyl.

The term “arylalkenyl” is used herein to mean any of the above-mentioned C₂₋₁₀ alkenyl groups substituted by any of the above-mentioned C₆₋₁₄ aryl groups.

The term “arylalkynyl” is used herein to mean any of the above-mentioned C₂₋₁₀ alkynyl groups substituted by any of the above-mentioned C₆₋₁₄ aryl groups.

The term “aryloxy” is used herein to mean oxygen substituted by one of the above-mentioned C₆₋₁₄ aryl groups, which may be optionally substituted. Useful aryloxy groups include phenoxy and 4-methylphenoxy.

The term “arylalkoxy” is used herein to mean any of the above mentioned C₁₋₁₀ alkoxy groups substituted by any of the above-mentioned aryl groups, which may be optionally substituted. Useful arylalkoxy groups include benzyloxy and phenethyloxy.

Useful haloalkyl groups include C₁₋₁₀ alkyl groups substituted by one or more fluorine, chlorine, bromine or iodine atoms, e.g., fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, chloromethyl, chlorofluoromethyl and trichloromethyl groups.

Useful acylamino (acylamido) groups are any C₁₋₆ acyl (alkanoyl) attached to an amino nitrogen, e.g., acetamido, chloroacetamido, propionamido, butanoylamido, pentanoylamido and hexanoylamido, as well as aryl-substituted C₁₋₆ acylamino groups, e.g., benzoylamido, and pentafluorobenzoylamido.

Useful acyloxy groups are any C₁₋₆ acyl (alkanoyl) attached to an oxy (—O—) group, e.g., formyloxy, acetoxy, propionyloxy, butanoyloxy, pentanoyloxy and hexanoyloxy.

The term heterocycle is used herein to mean a saturated or partially saturated 3-7 membered monocyclic, or 7-10 membered bicyclic ring system, which consists of carbon atoms and one to four heteroatoms independently selected from the group consisting of O, N, and S, wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, the nitrogen can be optionally quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, and wherein the heterocyclic ring can be substituted on carbon or on a nitrogen atom if the resulting compound is stable.

Useful saturated or partially saturated heterocyclic groups include tetrahydrofuranyl, pyranal, piperidinyl, piperazinyl, pyrrolidinyl, imidazolidinyl, imidazolyl, indolyl, isoindolyl, quinuclidinyl, morpholinyl, isochroman, chroman, pyrazolidinyl, pyrazolinyl, tetronoyl and tetramoyl groups.

The term “heteroaryl” as employed herein refers to groups having 5 to 14 ring atoms; 6, or 14 it electrons shared in a cyclic array; and containing, as ring atom, carbon atoms and 1-3 heteroatoms selected from oxygen, nitrogen and sulfur.

Useful heteroaryl groups include thienyl (thiophenyl), benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl (furanal), pyranal, isobenzofuranal, chromenyl, xanthenyl, phenoxanthiyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl (pyridinyl), including without limitation 2-pyridyl, 3-pyridyl, and 4-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, 4H-quinolizyl, isoquinolyl, quinolyl, phthalzyl, naphthridinyl, quinoxalyl, cinnolyl, pteridinyl, carbazolyl, (3-carbolyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl, phenoxazinyl, 1,4-dihydroquinoxaline-2,3-dione, 7-aminoisocoumarin, pyrido[1,2-a]pyrimidin-4-one, tetrahydrocyclopenta[c]pyrazol-3-yl, pyrazolo[1,5-a]pyrimidinyl, 1,2-benzisoxazol-3-yl, benzimidazolyl, 2-oxindolyl, thiadiazolyl, and 2-oxobenzimidazolyl. Where the heteroaryl group contains a nitrogen atom in a ring, such nitrogen atom may be in the form of an N-oxide, e.g., a pyridyl N-oxide, pyrazinyl N-oxide and pyrimidinyl N-oxide.

The term “heteroaryloxy” is used herein to mean oxygen substituted by one of the above-mentioned heteroaryl groups, which may be optionally substituted. Useful heteroaryloxy groups include pyridyloxy, pyrazinyloxy, pyrrolyloxy, pyrazolyloxy, imidazolyloxy and thiophenyloxy.

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The term "heteroarylalkoxy" is used herein to mean any of the above-mentioned C_{1-10} alkoxy groups substituted by any of the above-mentioned heteroaryl groups, which may be optionally substituted.

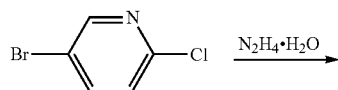
Some of the compounds of the present invention may exist as stereoisomers including optical isomers. The invention includes all stereoisomers and both the racemic mixtures of such stereoisomers as well as the individual enantiomers that may be separated according to methods that are well known to those of ordinary skill in the art.

Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts, such as hydrochloride, hydrobromide, phosphate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate and oxalate; and inorganic and organic base addition salts with bases, such as sodium hydroxy, Tris(hydroxymethyl)aminomethane (TRIS, tromethane) and N-methyl-glucamine.

Examples of prodrugs of the compounds of the invention include the simple esters of carboxylic acid containing compounds (e.g., those obtained by condensation with a C_{1-4} alcohol according to methods known in the art); esters of hydroxy containing compounds (e.g., those obtained by condensation with a C_{1-4} -carboxylic acid, C_{3-6} dioic acid or anhydride thereof, such as succinic and fumaric anhydrides according to methods known in the art); imines of amino containing compounds (e.g., those obtained by condensation with a C_{1-4} aldehyde or ketone according to methods known in the art); carbamate of amino containing compounds, such as those described by Leu, et. al., (*J. Med. Chem.* 42:3623-3628 (1999)) and Greenwald, et. al., (*J. Med. Chem.* 42:3657-3667 (1999)); and acetals and ketals of alcohol containing compounds (e.g., those obtained by condensation with chloromethyl methyl ether or chloromethyl ethyl ether according to methods known in the art).

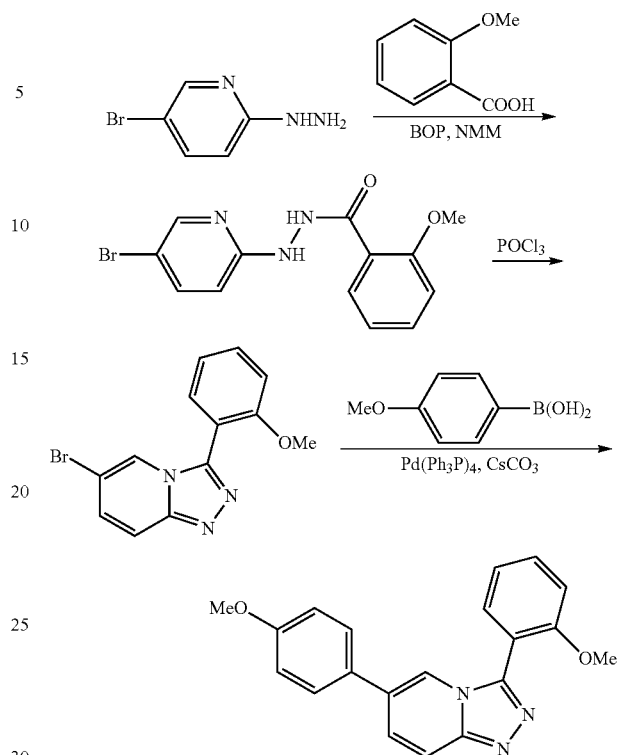
The compounds of this invention may be prepared using methods known to those skilled in the art, or the novel methods of this invention. Specifically, the compounds of this invention with Formula I or II can be prepared as illustrated by the exemplary reaction in Scheme 1. Reaction of a 2,5-dihalopyridine, such as 5-bromo-2-chloropyridine, and hydrazine produced 5-bromo-2-hydrazinylpyridine. Reaction of 5-bromo-2-hydrazinylpyridine with a substituted benzoic acid, such as 2-methoxybenzoic acid, in the presence of coupling agents, such as BOP and NMM, produced N-(5-bromopyridin-2-yl)-2-methoxybenzohydrazide. Treatment of N-(5-bromopyridin-2-yl)-2-methoxybenzohydrazide with phosphorus oxychloride produced the cyclized product 6-bromo-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine. Coupling of 6-bromo-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine with a substituted phenylboronic acid, such as 4-methoxyphenylboronic acid, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium, produced 3-(2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine.

Scheme 1



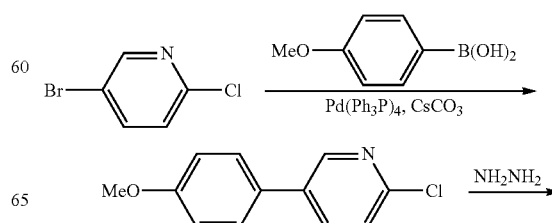
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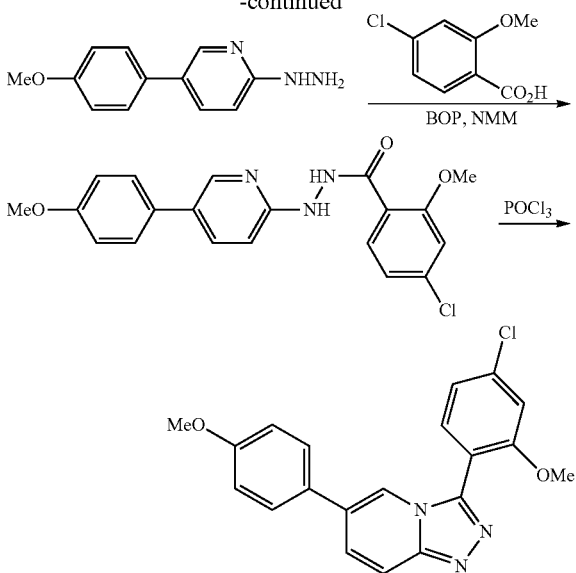
Compounds of this invention can be prepared as illustrated by the exemplary reaction in Scheme 2. Coupling of a 2,5-dihalopyridine, such as 5-bromo-2-chloropyridine, with a substituted phenylboronic acid, such as 4-methoxyphenylboronic acid, in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium, produced 2-chloro-5-(4-methoxyphenyl)pyridine. Reaction of 2-chloro-5-(4-methoxyphenyl)pyridine with hydrazine produced 2-hydrazinyl-5-(4-methoxyphenyl)pyridine. Reaction of 2-hydrazinyl-5-(4-methoxyphenyl)pyridine with a substituted benzoic acid, such as 4-chloro-2-methoxybenzoic acid, in the presence of coupling agents, such as BOP (benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate) and NMM (N-methylmorpholine), produced 4-chloro-2-methoxy-N-(5-(4-methoxyphenyl)pyridin-2-yl)-benzohydrazide. Treatment of 4-chloro-2-methoxy-N-(5-(4-methoxyphenyl)pyridin-2-yl)-benzohydrazide with phosphorus oxychloride produced the cyclized product 3-(4-chloro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine, which can be converted into a salt by treatment with HCl in ethyl acetate.

Scheme 2



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-continued



An important aspect of the present invention is the discovery that compounds having Formula I or II are antiproliferative agents. Therefore, these compounds are useful in a variety of clinical conditions in which there is uncontrolled cell proliferation and spread of abnormal cells, such as in the case of cancer.

Another important aspect of the present invention is the discovery that compounds having Formula I or II are potent and highly efficacious antiproliferative agents in drug resistant cancer cells, such as breast and prostate cancer cells, which enables these compounds to kill these drug resistant cancer cells. In comparison, many standard anticancer drugs are not effective in killing drug resistant cancer cells under the same conditions. Therefore, compounds of this invention are useful for the treatment of drug resistant cancer, such as breast cancer in mammals.

The present invention includes a therapeutic method comprising administering to a mammal an effective amount of a compound, or a pharmaceutically acceptable salt or prodrug of said compound of Formula I or II, wherein said therapeutic method is useful to treat cancer, which is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. Such diseases include, but are not limited to, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic leukemia, chronic lymphocytic leukemia, multiple myeloma, neuroblastoma, breast carcinoma, ovarian carcinoma, lung carcinoma, Wilms' tumor, cervical carcinoma, testicular carcinoma, soft-tissue sarcoma, primary macroglobulinemia, bladder carcinoma, chronic granulocytic leukemia, primary brain carcinoma, malignant melanoma, small-cell lung carcinoma, stomach carcinoma, colon carcinoma, malignant pancreatic insulinoma, malignant carcinoid carcinoma, choriocarcinoma, mycosis fungoides, head or neck carcinoma, osteogenic sarcoma, pancreatic carcinoma, acute granulocytic leukemia, hairy cell leukemia, neuroblastoma, rhabdomyosarcoma, Kaposi's sarcoma, genitourinary carcinoma, thyroid carcinoma, esophageal carcinoma, malignant hypercalcemia, cervical hyperplasia, renal cell carcinoma, endometrial carcinoma, polycythemia vera, essential thrombocytosis, adrenal cortex carcinoma, skin cancer, and prostatic carcinoma.

In practicing the therapeutic methods, effective amounts of compositions containing therapeutically effective concentra-

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tions of the compounds of Formula I or II formulated for oral, intravenous, local and topical application, for the treatment of neoplastic diseases and other diseases, are administered to an individual exhibiting the symptoms of one or more of these disorders. The amounts are effective to ameliorate or eliminate one or more symptoms of the disorders. An effective amount of a compound for treating a particular disease is an amount that is sufficient to ameliorate, or in some manner reduce, the symptoms associated with the disease. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective. The amount may cure the disease but, typically, is administered in order to ameliorate the symptoms of the disease. Typically, repeated administration is required to achieve the desired amelioration of symptoms.

In another embodiment, a pharmaceutical composition comprising a compound of Formula I or II or a pharmaceutically acceptable salt thereof, which functions as an antiproliferative agent, in combination with a pharmaceutically acceptable vehicle, is provided.

Another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound, or a pharmaceutically acceptable salt or prodrug of said compound of Formula I or II, which functions as an antiproliferative agent, in combination with at least one known anticancer agent, or a pharmaceutically acceptable salt of said agent. Examples of known anticancer agents which may be used for combination therapy include, but not are limited to alkylating agents, such as busulfan, cis-platin, mitomycin C, and carboplatin; antimetabolic agents, such as colchicine, vinblastine, paclitaxel, and docetaxel; topoisomerase I inhibitors, such as camptothecin and topotecan; topoisomerase II inhibitors, such as doxorubicin and etoposide; RNA/DNA antimetabolites, such as 5-azacytidine, 5-fluorouracil and methotrexate; DNA antimetabolites, such as 5-fluoro-2'-deoxy-uridine, ara-C, hydroxyurea and thioguanine; antibodies, such as campath, Herceptin®, Rituxan®. Other known anticancer agents which may be used for combination therapy include melphalan, chlorambucil, cyclophosphamide, ifosfamide, vincristine, mitoguanzone, epirubicin, aclarubicin, bleomycin, mitoxantrone, elliptinium, fludarabine, octreotide, retinoic acid, tamoxifen, arsenic trioxide, gemcitabine, letrozole, fulvestrant, bendamustine, pralatrexate, pemetrexed, nelarabine, temozolomide, zoledronic acid, irinotecan, ixabepilone, cabazitaxel, vinorelbine, Panitumumab, Ofatumumab, Avastin, imatinib, gefitinib, erlotinib, lapatinib, sorafenib, sunitinib, nilotinib, dasatinib, pazopanib, bortezomib, vorinostat, romidepsin, temsirolimus, everolimus, thalidomide, lenalidomide and alanosine.

In practicing the methods of the present invention, the compound of the invention may be administered together with at least one known anticancer agent as part of a unitary pharmaceutical composition. Alternatively, the compound of the invention may be administered apart from at least one known anticancer agent. In one embodiment, the compound of the invention and at least one known anticancer agent are administered substantially simultaneously, i.e. the compounds are administered at the same time or one after the other, so long as the compounds reach therapeutic levels in the blood at the same time. In another embodiment, the compound of the invention and at least one known anticancer agent are administered according to their individual dose schedule, so long as the compounds reach therapeutic levels in the blood.

Another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a

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bioconjugate of a compound described herein, which functions as an antiproliferative agent, in bioconjugation with at least one known therapeutically useful antibody, such as Herceptin® or Rituxan®, growth factors, such as DGF, NGF; cytokines, such as IL-2, IL-4, or any molecule that binds to the cell surface. The antibodies and other molecules will deliver a compound described herein to its targets and make it an effective anticancer agent. The bioconjugates could also enhance the anticancer effect of therapeutically useful antibodies, such as Herceptin® or Rituxan®.

Similarly, another embodiment of the present invention is directed to a composition effective to inhibit neoplasia comprising a compound of Formula I or II, or its pharmaceutically acceptable salt or prodrug, which functions as an antiproliferative agent, in combination with radiation therapy. In this embodiment, the compound of the invention may be administered at the same time as the radiation therapy is administered or at a different time.

Yet another embodiment of the present invention is directed to a composition effective for post-surgical treatment of cancer, comprising a compound of Formula I or II, or its pharmaceutically acceptable salt or prodrug, which functions as an antiproliferative agent. The invention also relates to a method of treating cancer by surgically removing the cancer and then treating the mammal with one of the pharmaceutical compositions described herein.

Stent implantation has become the new standard angioplasty procedure. However, in-stent restenosis remains the major limitation of coronary stenting. New approaches have been developed to target pharmacological modulation of local vascular biology by local administration of drugs. This allows for drug applications at the precise site and time of vessel injury. Numerous pharmacological agents with antiproliferative properties are currently under clinical investigation, including actinomycin D, rapamycin or paclitaxel coated stents (Regar E., et al., *Br. Med. Bull.* 59:227-248 (2001)). Therefore, antiproliferative agents of the present invention are useful as therapeutics for the prevention or reduction of in-stent restenosis.

Pharmaceutical compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount that is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the compounds may be administered to mammals, orally at a dose of 0.0025 to 50 mg/kg of body weight, per day, or an equivalent amount of the pharmaceutically acceptable salt thereof, to a mammal being treated. Preferably, approximately 0.01 to approximately 10 mg/kg of body weight is orally administered. If a known anticancer agent is also administered, it is administered in an amount that is effective to achieve its intended purpose. The amounts of such known anticancer agents effective for cancer are well known to those skilled in the art.

The unit oral dose may comprise from approximately 0.01 to approximately 50 mg, preferably approximately 0.1 to approximately 10 mg of the compound of the invention. The unit dose may be administered one or more times daily, as one or more tablets, each containing from approximately 0.1 to approximately 50 mg, conveniently approximately 0.25 to 10 mg of the compound or its solvates.

In a topical formulation, the compound may be present at a concentration of approximately 0.01 to 100 mg per gram of carrier.

In addition to administering the compound as a raw chemical, the compounds of the invention may be administered as

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part of a pharmaceutical preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the compounds into preparations that may be used pharmaceutically. Preferably, the preparations, particularly those preparations which may be administered orally and that may be used for the preferred type of administration, such as tablets, dragees, and capsules, as well as suitable solutions for administration by injection or orally, contain from approximately 0.01 to 99 percent, preferably from approximately 0.25 to 75 percent of active compound(s), together with the excipient.

Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the compounds of the present invention. Acid addition salts are formed by mixing a solution of the compounds of the present invention with a solution of a pharmaceutically acceptable non-toxic acid, such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, and the like. Basic salts are formed by mixing a solution of the compounds of the present invention with a solution of a pharmaceutically acceptable non-toxic base, such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, Tris, N-methyl-glucamine and the like.

The pharmaceutical compositions of the invention may be administered to any mammal, which may experience the beneficial effects of the compounds of the invention. Foremost among such mammals are humans and veterinary animals, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal, intrathecal, intracranial, intranasal or topical routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

The pharmaceutical preparations of the present invention are manufactured in a manner, which is itself known, e.g., by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use may be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular: fillers, such as saccharides, e.g. lactose or sucrose, mannitol or sorbitol; cellulose preparations and/or calcium phosphates, e.g. tricalcium phosphate or calcium hydrogen phosphate; as well as binders, such as starch paste, using, e.g., maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added, such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, e.g., silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide,

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lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, e.g., for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations, which may be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active compounds in the form of: granules, which may be mixed with fillers, such as lactose; binders, such as starches; and/or lubricants, such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, e.g., water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, e.g., sesame oil, or synthetic fatty acid esters, e.g., ethyl oleate or triglycerides or polyethylene glycol-400, or cremophor, or cyclodextrins. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, e.g., sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

In accordance with one aspect of the present invention, compounds of the invention are employed in topical and parenteral formulations and are used for the treatment of skin cancer.

The topical compositions of this invention are formulated preferably as oils, creams, lotions, ointments and the like by choice of appropriate carriers. Suitable carriers include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohol (greater than C_{12}). The preferred carriers are those in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included, as well as agents imparting color or fragrance, if desired. Additionally, transdermal penetration enhancers may be employed in these topical formulations. Examples of such enhancers are found in U.S. Pat. Nos. 3,989,816 and 4,444,762.

Creams are preferably formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture of the active ingredient, dissolved in a small amount of an oil, such as almond oil, is admixed. A typical example of such a cream is one which includes approximately 40 parts water, approximately 20 parts beeswax, approximately 40 parts mineral oil and approximately 1 part almond oil.

Ointments may be formulated by mixing a solution of the active ingredient in a vegetable oil, such as almond oil, with warm soft paraffin and allowing the mixture to cool. A typical example of such an ointment is one which includes approximately 30% almond oil and approximately 70% white soft paraffin by weight.

The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical

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therapy and which are obvious to those skilled in the art are within the spirit and scope of the invention.

EXAMPLES

General Remarks

All reagents were of commercial quality. Solvents were dried and purified by standard methods. Mass spectrum analyses were recorded on a Platform II (Agilent 6110) quadrupole mass spectrometer fitted with an electrospray interface. ^1H spectra was recorded at 300 MHz and at 300° K, on a Bruker AMX 300 apparatus. Chemical shifts were recorded as parts per million (ppm) downfield from TMS (0.00 ppm), and J coupling constants were reported in hertz (Hz).

Example 1

3-(2-Methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

a) 5-Bromo-2-hydrazinylpyridine

A mixture of 5-bromo-2-chloropyridine (11.5 g, 60 mmol) and hydrazine hydrate (100 mL) was refluxed under Argon for 2 h. The mixture was cooled to room temperature, filtered and the solids were washed with water (50 mL \times 3), dried to give the title compound (8.30 g, 74.4% yield) as yellow solids. MS: m/z 188.0 $[\text{M}+\text{H}^+]$.

b)

N-(5-Bromopyridin-2-yl)-2-methoxybenzohydrazide

To a solution of 5-bromo-2-hydrazinylpyridine (7.1 g, 38 mmol) and 2-methoxybenzoic acid (7.0 g, 46 mmol) in dichloromethane (DCM, 100 mL) were added benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP, 25.2 g, 57 mmol) and N-methylmorpholine (NMM, 13.4 g, 0.10 mol), and it was stirred at room temperature for 2 h. The mixture was filtered and the solids were washed with DCM (50 mL \times 3), dried to give the title compound (8.23 g, 67.5% yield) as yellow solids. MS: m/z 322.1 $[\text{M}+\text{H}^+]$.

c) 6-Bromo-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

A flask was charged with N-(5-bromopyridin-2-yl)-2-methoxybenzohydrazide (5.0 g, 15.6 mmol) and phosphorus oxychloride (POCl_3 , 50 mL). The mixture was stirred at 100° C. for 10 h, and then was added to about 200 g of ice. The mixture was adjusted to pH 9 with solid sodium bicarbonate (NaHCO_3). The precipitate was collected by filtration to give the crude product. The crude product was purified by column chromatography on silica gel (petroleum ether:ethyl acetate=1:1) to give the title compound (2.8 g, 59% yield) as yellow solids. ^1H NMR ($\text{DMSO}-d_6$): 8.28 (m, 1H), 7.86 (dd, J=9.6 and 0.9 Hz, 1H), 7.65-7.52 (m, 3H), 7.30 (d, J=8.1 Hz, 1H), 7.19 (m, 1H), 3.84 (s, 3H).

d) 3-(2-Methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

A flask was charged with 6-bromo-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (151 mg, 0.5 mmol), 4-methoxyphenylboronic acid (80 mg, 0.5 mmol), tetrakis(triph-

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enylphosphine)palladium (Pd(PPh₃)₄, 5.8 mg, 0.005 mmol), cesium carbonate (Cs₂CO₃, 326 mg, 1.0 mmol), 1,4-dioxane (10 mL) and water (2 mL). The mixture was stirred at 100° C. under Argon for 10 h. The mixture was evaporated to afford the crude product. The crude product was purified by column chromatography on silica gel (petroleum ether:ethyl acetate=1:1) to give the title compound (140 mg, 84.2% yield) as yellow solids. ¹H NMR (DMSO-d₆): 8.06 (m, 1H), 7.90 (dd, J=9.5 and 0.9 Hz, 1H), 7.75 (dd, J=9.6 and 1.8 Hz, 1H), 7.67-7.62 (m, 4H), 7.32 (d, J=8.1 Hz, 1H), 7.19 (t, J=7.5 Hz, 1H), 7.03 (d, J=8.7 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 3H). MS: m/z 332.2 [M+H⁺].

The following compounds were prepared from 6-bromo-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine and the corresponding phenylboronic acid, or pyridylboronic acid, or pyrimidylboronic acid using a procedure similar to those described for the synthesis of Example 1d.

Example 2

3-(2-Methoxyphenyl)-6-(3-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.16 (m, 1H), 7.94 (dd, J=9.6 and 1.2 Hz, 1H), 7.79 (dd, J=9.6 and 1.5 Hz, 1H), 7.67-7.61 (m, 2H), 7.43-7.17 (m, 5H), 6.99 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H). MS: m/z 332.2 [M+H⁺].

Example 3

3,6-Bis(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 7.93 (m, 1H), 7.86 (dd, J=9.6 and 1.2 Hz, 1H), 7.65-7.56 (m, 3H), 7.44-7.35 (m, 2H), 7.29 (d, J=8.1 Hz, 1H), 7.20-7.14 (m, 2H), 7.05 (m, 1H), 3.84 (s, 3H), 3.79 (s, 3H). MS: m/z 332.2 [M+H⁺].

Example 4

6-(2-Fluoro-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.07 (s, 1H), 7.94 (d, J=9.6 and 1.2 Hz, 1H), 7.63-7.61 (m, 3H), 7.50 (t, J=8.1 Hz, 1H), 7.30 (d, J=8.1 Hz, 1H), 7.21-7.13 (m, 3H), 3.83 (s, 3H), 2.36 (s, 3H). MS: m/z 334.2 [M+H⁺].

Example 5

6-(4-Methoxy-3-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.04 (m, 1H), 7.91 (dd, J=9.6 and 0.9 Hz, 1H), 7.75 (dd, J=9.6 and 1.5 Hz, 1H), 7.68-7.62 (m, 2H), 7.53-7.49 (m, 2H), 7.32 (d, J=8.1 Hz, 1H), 7.20 (t, J=8.0 Hz, 1H), 7.03 (d, J=9.0 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.21 (s, 3H). MS: m/z 346.2 [M+H⁺].

Example 6

6-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.05 (m, 1H), 7.91 (dd, J=9.6 and 0.9 Hz, 1H), 7.75 (dd, J=9.6 and 1.5 Hz, 1H), 7.64-7.59 (m,

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4H), 7.32 (d, J=8.4 Hz, 1H), 7.19 (t, J=7.5 Hz, 1H), 7.01 (d, J=9.0 Hz, 2H), 4.66 (m, 1H), 3.85 (s, 3H), 1.28 (d, J=6.0 Hz, 6H). MS: m/z 360.2 [M+H⁺].

Example 7

6-(4-Ethylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.10 (m, 1H), 7.94 (dd, J=9.5 and 1.2 Hz, 1H), 7.77 (dd, J=10.5 and 1.8 Hz, 1H), 7.64-7.60 (m, 4H), 7.34-7.30 (m, 3H), 7.19 (t, J=7.5 Hz, 1H), 3.85 (s, 3H), 2.65 (q, J=7.5 Hz, 2H), 1.20 (t, J=7.5 Hz, 3H). MS: m/z 330.2 [M+H⁺].

Example 8

6-(4-Methoxy-2-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 7.87 (dd, J=9.3 and 1.2 Hz, 1H), 7.77 (m, 1H), 7.64-7.59 (m, 2H), 7.42 (dd, J=9.5 and 1.5 Hz, 1H), 7.26 (d, J=8.1 Hz, 1H), 7.21-7.14 (m, 2H), 6.91 (m, 1H), 6.84 (m, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 2.29 (s, 3H). MS: m/z 346.2 [M+H⁺].

Example 9

6-(4-Benzoyloxy-3-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.13 (m, 1H), 7.91 (dd, J=9.6 and 1.8 Hz, 1H), 7.78 (dd, J=9.6 and 1.8 Hz, 1H), 7.67-7.61 (m, 2H), 7.47-7.11 (m, 10H), 5.14 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H). MS: m/z 438.2 [M+H⁺].

Example 10

3-(2-Methoxyphenyl)-6-(4-methyl-3-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.36 (m, 1H), 8.30 (d, J=1.8 Hz, 1H), 8.01-7.95 (m, 2H), 7.84 (dd, J=9.6 and 1.2 Hz, 1H), 7.68-7.59 (m, 3H), 7.22 (d, J=8.1 Hz, 1H), 7.20 (t, J=7.5 Hz, 1H), 3.85 (s, 3H), 2.54 (s, 3H). MS: m/z 361.2 [M+H⁺].

Example 11

3-(2-Methoxyphenyl)-6-(4-trifluoromethoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.22 (m, 1H), 7.96 (dd, J=9.6 and 1.2 Hz, 1H), 7.86-7.80 (m, 3H), 7.68-7.62 (m, 2H), 7.47 (d, J=8.1 Hz, 2H), 7.31 (d, J=8.1 Hz, 1H), 7.19 (t, J=8.0 Hz, 1H), 3.85 (s, 3H). MS: m/z 386.1 [M+H⁺].

Example 12

6-(3-Hydroxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 9.64 (s, 1H), 8.02 (m, 1H), 7.93 (dd, J=9.6 and 0.9 Hz, 1H), 7.74-7.61 (m, 3H), 7.32 (m, 1H), 7.27 (d, J=7.8 Hz, 1H), 7.20 (m, 1H), 7.10 (m, 1H), 7.02 (t, J=2.0 Hz, 1H), 6.83-6.80 (m, 1H), 3.86 (s, 3H). MS: m/z 318.1 [M+H⁺].

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Example 13

6-(4-Hydroxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]
triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 9.66 (s, 1H), 7.99 (m, 1H), 7.89 (dd, J=9.6 and 0.9 Hz, 1H), 7.72 (dd, J=9.6 and 1.8 Hz, 1H), 7.64-7.60 (m, 2H), 7.51 (d, J=6.6 Hz, 2H), 7.33 (d, J=8.1 Hz, 1H), 7.19 (t, J=7.2 Hz, 1H), 6.86 (d, J=6.6 Hz, 2H), 3.85 (s, 3H). MS: m/z 318.2 [M+H⁺].

Example 14

6-(Benzo[d][1,3]dioxol-5-yl)-3-(2-methoxyphenyl)-
[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.08 (m, 1H), 7.90 (dd, J=9.6 and 0.9 Hz, 1H), 7.73 (dd, J=9.6 and 1.8 Hz, 1H), 7.67-7.60 (m, 2H), 7.32-7.29 (m, 2H), 7.21-7.17 (m, 2H), 7.01 (d, J=8.1 Hz, 1H), 6.07 (s, 2H), 3.84 (s, 3H). MS: m/z 346.2 [M+H⁺].

Example 15

3-(2-Methoxyphenyl)-6-(6-methoxypyridin-3-yl)-[1,
2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.51 (d, J=2.1 Hz, 1H), 8.22 (s, 1H), 8.06 (dd, J=8.7 and 1.8 Hz, 1H), 7.95 (dd, J=9.6 and 0.9 Hz, 1H), 7.77 (dd, J=9.6 and 1.5 Hz, 1H), 7.67-7.62 (m, 2H), 7.31 (d, J=8.1 Hz, 1H), 7.19 (t, J=7.7 Hz, 1H), 6.93 (d, J=8.1 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H). MS: m/z 333.2 [M+H⁺].

Example 16

6-(4-Ethoxy-3-methylphenyl)-3-(2-methoxyphenyl)-
[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.03 (s, 1H), 7.90 (d, J=8.7 Hz, 1H), 7.75 (m, 1H), 7.68-7.62 (m, 2H), 7.49-7.46 (m, 2H), 7.32 (d, J=8.1 Hz, 1H), 7.19 (t, J=8.0 Hz, 1H), 7.01 (d, J=9.0 Hz, 1H), 4.07 (q, J=6.9 Hz, 2H), 3.86 (s, 3H), 2.21 (s, 3H), 1.36 (t, J=6.9 Hz, 3H). MS: m/z 360.2 [M+H⁺].

Example 17

6-(4-Dimethylaminophenyl)-3-(2-methoxyphenyl)-
[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 7.96 (m, 1H), 7.88 (dd, J=9.6 and 0.9 Hz, 1H), 7.75 (dd, J=9.6 and 1.8 Hz, 1H), 7.68-7.60 (m, 2H), 7.55-7.50 (m, 2H), 7.32 (d, J=8.1 Hz, 1H), 7.19 (t, J=7.5 Hz, 1H), 6.83-6.77 (m, 2H), 3.86 (s, 3H), 2.94 (s, 6H). MS: m/z 345.2 [M+H⁺].

Example 18

3-(2-Methoxyphenyl)-6-(2-methoxypyrimidin-5-yl)-
[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.95 (s, 2H), 8.42 (m, 1H), 7.99 (dd, J=9.6 and 0.9 Hz, 1H), 7.80 (dd, J=9.6 and 1.5 Hz, 1H),

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7.67-7.64 (m, 2H), 7.30 (d, J=8.1 Hz, 1H), 7.18 (t, J=7.1 Hz, 1H), 3.97 (s, 3H), 3.86 (s, 3H). MS: m/z 334.1 [M+H⁺].

Example 19

6-(3-Chloro-4-methylphenyl)-3-(2-methoxyphenyl)-
[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.23 (m, 1H), 7.93 (dd, J=9.6 and 1.5 Hz, 1H), 7.81-7.77 (m, 2H), 7.68-7.61 (m, 3H), 7.51 (m, 1H), 7.32 (d, J=7.8 Hz, 1H), 7.20 (m, 1H), 3.84 (s, 3H), 2.37 (s, 3H). MS: m/z 350.1 [M+H⁺].

Example 20

6-(3-Hydroxy-4-methoxyphenyl)-3-(2-methoxyphenyl)-
[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 9.23 (s, 1H), 7.94-7.88 (m, 2H), 7.72-7.61 (m, 3H), 7.33 (d, J=8.1 Hz, 1H), 7.20 (t, J=7.5 Hz, 1H), 7.11-7.00 (m, 3H), 3.86 (s, 3H), 3.80 (s, 3H). MS: m/z 348.2 [M+H⁺].

Example 21

6-(3-Methoxy-4-nitrophenyl)-3-(2-methoxyphenyl)-
[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.42 (m, 1H), 8.02-7.97 (m, 2H), 7.85 (m, 1H), 7.68-7.57 (m, 3H), 7.45 (m, 1H), 7.32 (m, 1H), 7.21 (m, 1H), 4.04 (s, 3H), 3.89 (s, 3H). MS: m/z 377.1 [M+H⁺].

Example 22

3-(2-Methoxyphenyl)-6-(4-methylphenyl)-[1,2,4]
triazolo[4,3-a]pyridine

To a solution of 6-bromo-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (100 mg, 0.329 mmol) in toluene (20 mL) and water (5 mL) was added 4-methylphenylboronic acid (67.1 mg, 0.493 mmol), Pd(PPh₃)₄ (18.4 mg, 0.016 mmol) and Cs₂CO₃ (55.3 mg, 0.658 mmol), and the reaction mixture was refluxed under Argon overnight. The mixture was filtered and the filtrate was washed with water (50 mL×2), dried over anhydrous Na₂SO₄ and concentrated to dryness. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate=1:1) to give the title compound (89.5 mg, 50.6% yield) as yellow solids. ¹H NMR (DMSO-d₆): 8.09 (m, 1H), 7.93 (dd, J=9.6 and 0.9 Hz, 1H), 7.77 (d, J=9.6 and 1.8 Hz, 1H), 7.64-7.58 (m, 4H), 7.33-7.28 (m, 3H), 7.19 (t, J=7.2 Hz, 1H), 3.85 (s, 3H), 2.35 (s, 3H). MS: m/z 316.2 [M+H⁺].

The following compounds were prepared from 6-bromo-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine and the corresponding phenylboronic acid using a procedure similar to those described for the synthesis of Example 22.

Example 23

3-(2-Methoxyphenyl)-6-(3-methylphenyl)-[1,2,4]
triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.11 (m, 1H), 7.93 (dd, J=9.6 and 0.9 Hz, 1H), 7.77 (d, J=9.6 and 1.8 Hz, 1H), 7.63 (m, 2H),

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7.51-7.47 (m, 2H), 7.40-7.31 (m, 2H), 7.25-7.17 (m, 2H), 3.86 (s, 3H), 2.37 (s, 3H). MS: m/z 316.2 [M+H⁺].

Example 24

3-(2-Methoxyphenyl)-6-phenyl-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.14 (m, 1H), 7.95 (dd, J=9.6 and 1.2 Hz, 1H), 7.79 (dd, J=9.6 and 1.8 Hz, 1H), 7.72-7.62 (m, 4H), 7.52-7.42 (m, 3H), 7.32 (d, J=7.8 Hz, 1H), 7.17 (t, J=8.0 Hz, 1H), 3.86 (s, 3H). MS: m/z 302.2 [M+H⁺].

Example 25

6-(2,4-Dimethylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 7.88 (dd, J=9.6 and 0.9 Hz, 1H), 7.79 (m, 1H), 7.62-7.59 (m, 2H), 7.43 (dd, J=9.6 and 1.8 Hz, 1H), 7.26 (d, J=8.1 Hz, 1H), 7.19-7.14 (m, 3H), 7.08 (d, J=7.5 Hz, 1H), 3.82 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H). MS: m/z 330.2 [M+H⁺].

Example 26

6-(3-Chloro-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.19 (s, 1H), 7.92 (d, J=9.6 Hz, 1H), 7.82-7.76 (m, 2H), 7.69-7.62 (m, 3H), 7.33-7.17 (m, 3H), 3.90 (s, 3H), 3.84 (s, 3H). MS: m/z 366.1 [M+H⁺].

Example 27

3-(2-Methoxyphenyl)-6-(4-trifluoromethylphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.31 (s, 1H), 8.01-7.94 (m, 3H), 7.85-7.82 (m, 3H), 7.68-7.63 (m, 2H), 7.32 (d, J=9.0 Hz, 1H), 7.17 (t, J=7.5 Hz, 1H), 3.85 (s, 3H). MS: m/z 370.1 [M+H⁺].

Example 28

6-(3-Methoxy-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.15 (m, 1H), 7.93 (dd, J=9.6 and 0.9 Hz, 1H), 7.80 (dd, J=9.6 and 1.8 Hz, 1H), 7.67-7.61 (m, 2H), 7.32 (d, J=8.1 Hz, 1H), 7.25-7.14 (m, 4H), 3.88 (s, 6H), 2.18 (s, 3H). MS: m/z 346.2 [M+H⁺].

Example 29

3-(2-Methoxyphenyl)-6-(3,4,5-trimethoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.20 (m, 1H), 7.93 (dd, J=9.6 and 0.9 Hz, 1H), 7.81 (dd, J=9.6 and 1.8 Hz, 1H), 7.67-7.62 (m, 2H), 7.32 (d, J=8.1 Hz, 1H), 7.19 (t, J=7.5 Hz, 1H), 6.93 (s, 2H), 3.92 (s, 3H), 3.87 (s, 6H), 3.69 (s, 3H). MS: m/z 392.2 [M+H⁺].

Example 30

6-(3,5-Dimethyl-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.11 (m, 1H), 7.96 (dd, J=9.6 and 0.9 Hz, 1H), 7.79 (dd, J=9.6 and 1.8 Hz, 1H), 7.70-7.67 (m,

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2H), 7.41-7.36 (m, 3H), 7.25 (t, J=8.0 Hz, 1H), 3.91 (s, 3H), 3.73 (s, 3H), 2.33 (s, 6H). MS: m/z 360.2 [M+H⁺].

Example 31

6-(3,4-Dimethoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.12 (m, 1H), 7.91 (dd, J=9.6 and 0.9 Hz, 1H), 7.78 (dd, J=9.6 and 1.5 Hz, 1H), 7.66-7.61 (m, 2H), 7.31 (d, J=8.4 Hz, 1H), 7.23-7.16 (m, 3H), 7.05 (d, J=8.4 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H). MS: m/z 362.2 [M+H⁺].

Example 32

6-(3,4-Dimethylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.07 (m, 1H), 7.92 (dd, J=9.6 and 0.9 Hz, 1H), 7.75 (dd, J=9.6 and 1.8 Hz, 1H), 7.64-7.62 (m, 2H), 7.47 (s, 1H), 7.40 (d, J=8.0 Hz, 1H), 7.31 (d, J=8.1 Hz, 1H), 7.24-7.16 (m, 2H), 3.85 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H). MS: m/z 330.2 [M+H⁺].

Example 33

6-(3-Fluoro-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.22 (m, 1H), 7.93 (dd, J=9.6 and 1.2 Hz, 1H), 7.79 (dd, J=9.6 and 1.5 Hz, 1H), 7.67-7.30 (m, 6H), 7.19 (t, J=7.5 Hz, 1H), 3.84 (s, 3H), 2.27 (s, 3H). MS: m/z 334.2 [M+H⁺].

Example 34

6-(4-Hexyloxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.04 (m, 1H), 7.91 (dd, J=9.6 and 0.9 Hz, 1H), 7.75 (dd, J=9.6 and 1.5 Hz, 1H), 7.63-7.60 (m, 4H), 7.31 (d, J=8.4 Hz, 1H), 7.19 (t, J=7.2 Hz, 1H), 7.02 (d, J=8.7 Hz, 2H), 4.00 (t, J=6.6 Hz, 2H), 3.85 (s, 3H), 1.76-1.67 (m, 2H), 1.44-1.28 (m, 6H), 0.88 (t, J=6.9 Hz, 3H). MS: m/z 402.2 [M+H⁺].

Example 35

6-(3-Fluoro-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.18 (m, 1H), 7.92 (dd, J=9.6 and 0.9 Hz, 1H), 7.78 (dd, J=9.6 and 1.8 Hz, 1H), 7.68-7.62 (m, 3H), 7.52 (m, 1H), 7.32-7.16 (m, 3H), 3.88 (s, 3H), 3.84 (s, 3H). MS: m/z 350.2 [M+H⁺].

Example 36

6-(2,4-Dimethoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 7.88-7.19 (m, 2H), 7.66-7.53 (m, 3H), 7.30 (d, J=8.4 Hz, 2H), 7.18 (t, J=7.5 Hz, 1H), 6.70 (d, J=2.4 Hz, 1H), 6.62 (dd, J=8.4 and 2.4 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H). MS: m/z 362.2 [M+H⁺].

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Example 37

6-(4-Benzyloxy-3-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.05 (s, 1H), 7.90 (d, J=9.6 Hz, 1H), 7.75 (d, J=9.6 Hz, 1H), 7.64-7.61 (m, 2H), 7.52-7.30 (m, 8H), 7.19 (t, J=8.1 Hz, 1H), 7.10 (d, J=8.4 Hz, 1H), 5.18 (s, 2H), 3.86 (s, 3H), 2.27 (s, 3H). MS: m/z 422.2 [M+H⁺].

Example 38

6-(4-Ethoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.05 (m, 1H), 7.91 (dd, J=9.6 and 1.2 Hz, 1H), 7.76 (dd, J=9.6 and 1.8 Hz, 1H), 7.67-7.61 (m, 4H), 7.32 (d, J=8.1 Hz, 1H), 7.19 (t, J=7.5 Hz, 1H), 7.02 (d, J=8.7 Hz, 2H), 4.06 (q, J=6.9 Hz, 2H), 3.85 (s, 3H), 1.34 (t, J=6.9 Hz, 3H). MS: m/z 346.2 [M+H⁺].

Example 39

3-(2-Methoxyphenyl)-6-(4-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.40 (s, 1H), 8.32-8.30 (m, 2H), 8.04-7.86 (m, 4H), 7.66-7.63 (m, 2H), 7.34-7.17 (m, 2H), 3.85 (s, 3H). MS: m/z 347.1 [M+H⁺].

Example 40

6-(4-Methoxy-3-nitrophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.37 (m, 1H), 8.31 (m, 1H), 8.09 (dd, J=9.0 and 2.4 Hz, 1H), 8.02 (d, J=9.6 Hz, 1H), 7.88 (dd, J=9.6 and 1.8 Hz, 1H), 7.71-7.69 (m, 2H), 7.52 (d, J=8.7 Hz, 1H), 7.38 (d, J=8.7 Hz, 1H), 7.26 (t, J=7.5 Hz, 1H), 4.03 (s, 3H), 3.91 (s, 3H). MS: m/z 377.1 [M+H⁺].

Example 41

6-(4-Hydroxy-3-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 9.58 (s, 1H), 7.96 (s, 1H), 7.88 (d, J=9.6 Hz, 1H), 7.72 (d, J=9.6 Hz, 1H), 7.67-7.60 (m, 2H), 7.40 (s, 1H), 7.35 (d, J=8.1 Hz, 2H), 7.19 (t, J=7.5 Hz, 1H), 6.86 (d, J=5.2 Hz, 1H), 3.85 (s, 3H), 2.17 (s, 3H). MS: m/z 332.2 [M+H⁺].

Example 42

6-(4-Methoxy-3-nitrophenyl)-3-(2-methoxy-5-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyridine

To a flask charged with 3-(2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (100 mg, 0.3 mmol) and concentrated sulfuric acid (H₂SO₄, 5 mL) kept in ice salt bath (-15° C.) was added nitric acid (HNO₃, 20 mg, 0.3 mmol), and it was stirred at -15° C. for 1 h. The reaction mixture was added to about 30 g of ice, and adjusted to pH=9 with solid NaHCO₃. The mixture was filtered and the solids were washed with methanol (10 mL×3), dried to give the title compound (50 mg, 37% yield) as yellow solids. ¹H NMR (DMSO-d₆): 8.56-8.47 (m, 3H), 8.25 (m, 1H), 7.98-8.07 (m,

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2H), 7.87 (dd, J=9.3 and 1.2 Hz, 1H), 7.55 (d, J=9.3 Hz, 1H), 7.47 (d, J=8.7 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H). MS: m/z 422.1 [M+H⁺].

Example 43

6-(4-Amino-3-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

A flask was charged with 6-(3-methoxy-4-nitrophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (100 mg, 0.27 mmol), stannous chloride dihydrate (SnCl₂, 300 mg, 1.35 mmol) and MeOH (10 mL). The mixture was stirred at 50° C. under Argon for 4 h. The pH of the mixture was adjusted to around 9 by progressively adding solid NaHCO₃, and it was evaporated to afford the crude product. The crude product was purified by column chromatography on silica gel (petroleum ether:ethyl acetate=1:1) to give the title compound (28.5 mg, 31.2% yield) as yellow solids. ¹H NMR (DMSO-d₆): 7.99 (s, 1H), 7.87 (d, J=9.6 Hz, 1H), 7.75 (d, J=9.6 Hz, 1H), 7.67-7.61 (m, 2H), 7.32 (d, J=8.4 Hz, 1H), 7.19 (t, J=7.5 Hz, 1H), 7.07 (d, J=1.8 Hz, 1H), 7.02 (dd, J=8.1 and 1.8 Hz, 1H), 6.71 (d, J=8.1 Hz, 1H), 5.00 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H). MS: m/z 347.2 [M+H⁺].

Example 44 was prepared from 3-(2-methoxyphenyl)-6-(4-methyl-3-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyridine using a procedure similar to those described for the synthesis of Example 43.

Example 44

6-(3-Amino-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 7.90-7.89 (m, 2H), 7.61-7.69 (m, 3H), 7.33 (d, J=8.1 Hz, 1H), 7.21 (t, J=7.5 Hz, 1H), 7.02 (d, J=8.4 Hz, 1H), 6.86 (d, J=1.8 Hz, 1H), 6.77 (dd, J=7.5 and 1.8 Hz, 1H), 5.01 (s, 2H), 3.86 (s, 3H), 2.08 (s, 3H). MS: m/z 331.2 [M+H⁺].

Example 45

6-(3-Aminophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride

a) 6-(3-(tert-Butoxycarbonylamino)phenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

The title compound was prepared from 6-bromo-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine and 3-(tert-butoxycarbonylamino)phenylboronic acid using a procedure similar to those described for the synthesis of Example 22, and was isolated as yellow solids (78 mg, 22.0% yield). MS: m/z 417.2 [M+H⁺].

b) 6-(3-Aminophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride

A mixture of 6-(3-(tert-butoxycarbonylamino)phenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (78 mg, 0.19 mmol) in HCl/ethyl acetate (2M, 20 mL) was stirred at room temperature for about 3 h. The mixture was concentrated under reduced pressure to give the crude compound. It was recrystallized in MeOH/ethyl acetate to give the title compound (9.8 mg, 15% yield) as yellow solids. ¹H NMR (DMSO-d₆): 8.36 (s, 1H), 8.16 (d, J=8.1 Hz, 1H), 8.05 (d,

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J=8.1 Hz, 1H), 7.78-7.60 (m, 5H), 7.49 (d, J=6.9 Hz, 1H), 7.37 (d, J=7.8 Hz, 1H), 7.23 (t, J=6.6 Hz, 1H), 3.92 (s, 3H). MS: m/z 317.2 [M+H⁺].

Example 46

6-(3-Amino-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride

A mixture of 6-(4-methoxy-3-nitrophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (80 mg, 0.21 mmol), iron (59 mg, 1.06 mmol) and NH₄Cl (6 mg, 0.11 mmol) in ethanol (10 mL) and water (10 mL) was stirred for 3 h at 70° C. The mixture was concentrated under reduced pressure at 50° C. to remove ethanol, and was extracted with ethyl acetate (40 mL×4). The combined organic phase were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to give a product. The product was dissolved in HCl/ethyl acetate (2M, 20 mL), stirred at room temperature for 30 min, and concentrated to dryness to give the title compound (7.45 mg, 10.2% yield) as yellow solids. ¹H NMR (DMSO-d₆): 8.14 (m, 1H), 8.05 (dd, J=9.6 and 0.9 Hz, 1H), 7.88 (dd, J=9.6 and 1.5 Hz, 1H), 7.71-7.58 (m, 4H), 7.35 (d, J=8.1 Hz, 1H), 7.26-7.19 (m, 2H), 3.92 (s, 3H), 3.89 (s, 3H). MS: m/z 347.2 [M+H⁺].

Example 47 was prepared from 3-(2-methoxyphenyl)-6-(4-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyridine using a procedure similar to those described for the synthesis of Example 46.

Example 47

6-(4-Aminophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride

¹H NMR (DMSO-d₆): 8.44 (s, 1H), 8.14 (s, 2H), 7.84 (d, J=8.7 Hz, 2H), 7.74-7.65 (m, 2H), 7.46 (d, J=8.7 Hz, 2H), 7.36 (d, J=8.1 Hz, 1H), 7.23 (t, J=7.2 Hz, 1H), 3.88 (s, 3H). MS: m/z 317.2 [M+H⁺].

Example 48

6-(4-Methylaminophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride

a) 6-(4-(t-Butylcarbonylamino)phenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

A mixture of 6-(4-aminophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (110 mg, 0.31 mmol), di-tert-butylidicarbonate (126 mg, 1.25 mmol) and triethylamine in DCM (40 mL) was stirred at room temperature overnight. The mixture was washed with water and extracted with ethyl acetate (100 mL×4). The combined organic phase were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to give the title compound (120 mg, 93.0% yield) as yellow solids. MS: m/z 417.2 [M+H⁺].

b) 6-(4-(N-Methyl-t-butylcarbonylamino)phenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

To a mixture of 6-(4-t-butylcarbonylamino)phenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (120 mg, 0.29 mmol) in dry THF (20 mL) cooled at 0° C. was added NaH (12 mg, 0.32 mmol), and it was stirred for 2 h. To the mixture was added iodomethane (164 mg, 1.5 mmol) in THF (8 mL) dropwise, and the mixture was stirred at room tem-

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perature overnight. The reaction mixture was quenched with saturated NH₄Cl (20 mL) and extracted with ethyl acetate (100 mL×3). The combined organic phase was dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated and the residue was purified by preparative TLC to give the title compound (38 mg, 31% yield) as yellow solids. MS: m/z 431.3 [M+H⁺].

c) 6-(4-Methylaminophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride

The title compound was prepared from 6-(4-(N-methyl-t-butylcarbonylamino)phenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine using a procedure similar to those described for the synthesis of Example 45b, and was isolated as yellow solids. ¹H NMR (DMSO-d₆): 8.34 (s, 1H), 8.18-8.09 (m, 2H), 7.73-7.65 (m, 4H), 7.36 (d, J=8.4 Hz, 1H), 7.26-7.13 (m, 3H), 3.88 (s, 3H), 2.82 (s, 3H). MS: m/z 331.1 [M+H⁺].

Example 49

3-(4-Chloro-2-methoxyphenyl)-6-(3-fluoro-4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

a) 6-Chloro-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

The title compound was prepared from 2,5-dichloropyridine and 2-methoxy-4-chlorobenzoic acid using procedures similar to those described for the synthesis of Examples 1a-1c, and was isolated as yellow solids. ¹H NMR (DMSO-d₆): 8.37 (s, 1H), 7.92 (dd, J=9.6 Hz, J=0.9 Hz, 1H), 7.60 (d, J=8.4 Hz, 1H), 7.49 (dd, J=9.6 Hz, J=1.8 Hz, 1H), 7.39 (s, 1H), 7.24 (dd, J=8.1 Hz, J=1.8 Hz, 1H), 3.86 (s, 3H). MS: m/z 294.0 [M+H⁺].

b) 3-(4-Chloro-2-methoxyphenyl)-6-(3-fluoro-4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

The title compound was prepared from 6-chloro-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine and 3-fluoro-4-methoxyphenylboronic acid using a procedure similar to those described for the synthesis of Example 1d, and was isolated as white solids. ¹H NMR (DMSO-d₆): 8.29 (m, 1H), 7.92 (dd, J=9.6 and 0.9 Hz, 1H), 7.80 (dd, J=9.6 and 1.8 Hz, 1H), 7.71-7.62 (m, 2H), 7.56 (m, 1H), 7.54 (t, J=1.2 Hz, 1H), 7.40-7.23 (m, 2H), 3.88 (s, 3H), 3.87 (s, 3H). MS: m/z 384.2 [M+H⁺].

Example 50 was prepared from 6-chloro-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine and 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline using a procedure similar to those described for the synthesis of Example 22.

Example 50

6-(3-Amino-4-methoxyphenyl)-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (CD₃OD): 7.94 (s, 1H), 7.83-7.76 (m, 2H), 7.61 (d, J=8.4 Hz, 1H), 7.34 (s, 1H), 7.24 (d, J=6.6 Hz, 1H), 6.99-6.90 (m, 3H), 4.09 (s, 3H), 3.88 (s, 3H). MS: m/z 381.1 [M+H⁺].

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Example 51

6-(3-Hydroxy-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine

a) 6-Chloro-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine

The title compound was prepared from 2,5-dichloropyridine and 2-methoxy-4-methylbenzoic acid using procedures similar to those described for the synthesis of Examples 1a-1c, and was isolated as yellow solids. MS: m/z 274.1 [M+H⁺].

b) 6-(3-Hydroxy-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine

The title compound was prepared from 6-chloro-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine and 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol using a procedure similar to those described for the synthesis of Example 1d, and was isolated as yellow solids. ¹H NMR (DMSO-d₆): 9.23 (s, 1H), 7.91-7.86 (m, 2H), 7.69 (dd, J=9.6 and 1.5 Hz, 1H), 7.49 (d, J=7.5 Hz, 1H), 7.16-6.99 (m, 5H), 3.84 (s, 3H), 3.80 (s, 3H), 2.45 (s, 3H). MS: m/z 362.2 [M+H⁺].

The following compounds were prepared from 6-chloro-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine and the corresponding substituted phenylboronic acid using a procedure similar to those described for the synthesis of Example 1d.

Example 52

6-(3-Amino-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (CD₃OD): 7.80 (s, 1H), 7.71 (d, J=9.3 Hz, 1H), 7.64 (d, J=9.3 Hz, 1H), 7.43 (d, J=7.8 Hz, 1H), 7.06 (s, 1H), 6.96 (d, J=7.8 Hz, 1H), 6.90 (s, 1H), 6.81 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 2.45 (s, 3H). MS: m/z 361.2 [M+H⁺].

Example 53

6-(3-Fluoro-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.11 (s, 1H), 7.86 (d, J=9.0 Hz, 1H), 7.74 (dd, J=9.6 and 1.5 Hz, 1H), 7.62 (dd, J=12.9 and 2.1 Hz, 1H), 7.50-7.43 (m, 2H), 7.23 (t, J=9.0 Hz, 1H), 7.11 (s, 1H), 6.98 (d, J=7.5 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 2.43 (s, 3H). MS: m/z 364.2 [M+H⁺].

Example 54

3-(2-Methoxyphenyl)-6-(4-methoxyphenyl)-7-methyl-[1,2,4]triazolo[4,3-a]pyridine

The title compound was prepared from 2,5-dibromo-4-methylpyridine, 2-methoxybenzoic acid and 4-methoxyphenylboronic acid using procedures similar to those described for the synthesis of Examples 1a-1d, and was isolated as yellow solids. ¹H NMR (DMSO-d₆): 7.75 (s, 1H), 7.64-7.57 (m, 3H), 7.34 (d, J=8.7 Hz, 2H), 7.25 (d, J=7.8 Hz, 1H), 7.16 (t, J=7.2 Hz, 1H), 7.02 (d, J=8.7 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 2.26 (s, 3H). MS: m/z 346.2 [M+H⁺].

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Example 55

3-(2-Methoxyphenyl)-6-(4-methoxyphenyl)-8-methyl-[1,2,4]triazolo[4,3-a]pyridine

The title compound was prepared from 2,5-dibromo-3-methylpyridine, 2-methoxybenzoic acid and 4-methoxyphenylboronic acid using procedures similar to those described for the synthesis of Examples 1a-1d, and was isolated as yellow solids. ¹H NMR (DMSO-d₆): 7.90 (s, 1H), 7.67-7.58 (m, 5H), 7.31 (d, J=8.1 Hz, 1H), 7.19 (t, J=6.9 Hz, 1H), 7.03 (d, J=9.0 Hz, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.65 (s, 3H). MS: m/z 346.2 [M+H⁺].

Example 56

6-(4-Hydroxy-3-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

The title compound was prepared from 2,5-dichloropyridine, 2-methoxybenzoic acid and 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol using procedures similar to those described for the synthesis of Examples 1a-1d. ¹H NMR (DMSO-d₆): 9.25 (s, 1H), 8.06 (m, 1H), 7.90 (dd, J=9.6 and 0.6 Hz, 2H), 7.76 (dd, J=9.6 and 1.5 Hz, 2H), 7.66-7.62 (m, 2H), 7.32 (d, J=8.4 Hz, 1H), 7.16-7.22 (m, 2H), 7.07-7.11 (m, 1H), 6.86 (d, J=8.1 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H). MS: m/z 348.2 [M+H⁺].

Example 57

3-(4-Chloro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

a) 2-Chloro-5-(4-methoxyphenyl)pyridine

A flask was charged with 4-methoxyphenylboronic acid (1.0 g, 6.8 mmol), 5-bromo-2-chloropyridine (1.0 g, 5.2 mmol), Pd(PPh₃)₄ (50 mg, 0.043 mmol), potassium carbonate (1.08 g, 7.8 mmol), 1,4-dioxane (40 mL) and water (4 mL). The mixture was stirred at 100° C. under Argon for 20 h, and evaporated to afford a crude product. The crude product was purified by chromatography on silica gel (petroleum ether:ethyl acetate=40:1) to give the title compound (1.0 g, 88% yield) as white solids. MS: m/z 220.0 [M+H⁺].

b) 2-Hydrazinyl-5-(4-methoxyphenyl)pyridine

A round-bottom flask was charged with 2-chloro-5-(4-methoxyphenyl)pyridine (260 mg, 1.19 mmol) and hydrazine hydrate (4 mL) at room temperature. The reaction mixture was heated at 100° C. for 48 h. It was cooled to room temperature, then was kept in a refrigerator for 3 h. The precipitate was filtered, washed with cold water, and dried to give the title compound as gray solids (200 mg, 78.0% yield). MS: m/z 216.1 [M+H⁺].

c) 4-Chloro-2-methoxy-N'-(5-(4-methoxyphenyl)pyridin-2-yl)-benzohydrazide

A solution of 2-hydrazinyl-5-(4-methoxyphenyl)pyridine (200 mg, 0.93 mmol), 4-chloro-2-methoxybenzoic acid (210 mg, 1.12 mmol), BOP (500 mg, 1.12 mmol) and NMM (330 mg, 3.27 mmol) in DCM (9 mL) was stirred at room temperature under Nitrogen overnight. The resulting mixture was filtered, and the solid was washed with DCM, dried to give the

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title compound as white solids (290 mg, 81.2% yield), which was used for the next reaction without further purification. MS: m/z 384.2 [M+H⁺].

d) 3-(4-Chloro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

A flask was charged with the crude 4-chloro-2-methoxy-N'-(5-(4-methoxyphenyl)pyridin-2-yl)-benzohydrazide and POCl₃ (13 mL), and the mixture was stirred at 80-100° C. overnight. The mixture was evaporated and the residue was adjusted to pH=9 with aqueous Na₂CO₃, then it was extracted with ethyl acetate (50 mL×4). The extract was dried over anhydrous Na₂SO₄ and the solvent was removed by evaporation. The crude product was purified by chromatography on silica (petroleum ether:ethyl acetate=1:1 to 0:1) to give the title compound as white solids (208 mg, 75.0% yield). ¹H NMR (DMSO-d₆): 8.17 (m, 1H), 7.92 (dd, J=9.6 and 1.2 Hz, 1H), 7.77 (dd, J=9.6 and 1.8 Hz, 1H), 7.68-7.62 (m, 3H), 7.40 (d, J=2.1 Hz, 1H), 7.25 (dd, J=8.1 and 2.1 Hz, 1H), 7.04 (d, J=6.6 Hz, 2H), 3.88 (s, 3H), 3.80 (s, 3H). MS: m/z 366.2 [M+H⁺].

The following compounds were prepared from 2-hydrazinyl-5-(4-methoxyphenyl)pyridine and the corresponding substituted benzoic acid using procedures similar to those described for the synthesis of Examples 57c-d.

Example 58

3-(4-Fluoro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.12 (s, 1H), 7.91 (d, J=9.6 Hz, 1H), 7.76 (d, J=9.6 Hz, 1H), 7.67-7.62 (m, 3H), 7.22 (dd, J=11.3 and 2.1 Hz, 1H), 7.05-7.00 (m, 3H), 3.85 (s, 3H), 3.79 (s, 3H). MS: m/z 350.2 [M+H⁺].

Example 59

3-(4-Bromo-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.18 (s, 1H), 7.92 (d, J=9.6 Hz, 1H), 7.77 (d, J=9.6 Hz, 1H), 7.67 (d, J=9.0 Hz, 2H), 7.57-7.51 (m, 2H), 7.39 (dd, J=8.1 and 1.5 Hz, 1H), 7.04 (d, J=9.0 Hz, 2H), 3.88 (s, 3H), 3.80 (s, 3H). MS: m/z 410.1 [M+H⁺].

Example 60

3-(2-Methoxy-4-trifluoromethylphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.27 (m, 1H), 7.95 (dd, J=9.6 and 0.9 Hz, 1H), 7.87-7.82 (m, 2H), 7.69 (d, J=8.7 Hz, 2H), 7.58 (s, 1H), 7.54 (d, J=7.8 Hz, 1H), 7.04 (d, J=9.0 Hz, 2H), 3.95 (s, 3H), 3.80 (s, 3H). MS: m/z 400.2 [M+H⁺].

Example 61

3-(2,6-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 7.90 (dd, J=9.5 and 1.2 Hz, 1H), 7.84 (m, 1H), 7.73 (dd, J=9.5 and 1.5 Hz, 1H), 7.62-7.57 (m, 3H), 7.02 (d, J=8.7 Hz, 2H), 6.89 (d, J=8.4 Hz, 2H), 3.95 (s, 3H), 3.79 (s, 3H), 3.71 (s, 3H). MS: m/z 362.2 [M+H⁺].

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Example 62

3-(2,5-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.04 (s, 1H), 7.91 (d, J=9.0 Hz, 1H), 7.76 (d, J=9.0 Hz, 1H), 7.63 (d, J=9.0 Hz, 2H), 7.23-7.17 (m, 3H), 7.04 (d, J=9.0 Hz, 2H), 3.79-3.78 (m, 9H). MS: m/z 362.2 [M+H⁺].

Example 63

3-(6-Fluoro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.10 (m, 1H), 7.95 (dd, J=9.0 and 0.9 Hz, 1H), 7.79 (dd, J=9.0 and 1.5 Hz, 1H), 7.72-7.64 (m, 3H), 7.17-7.02 (m, 4H), 4.03 (s, 3H), 3.80 (s, 3H). MS: m/z 350.2 [M+H⁺].

Example 64

3,6-Bis(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.46 (s, 1H), 7.93-7.89 (m, 3H), 7.75-7.68 (m, 3H), 7.19 (d, J=9.0 Hz, 2H), 7.06 (d, J=8.7 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 3H). MS: m/z 332.2 [M+H⁺].

Example 65

3-(3-Bromo-2,6-dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.09 (m, 1H), 7.93 (dd, J=9.6 and 0.9 Hz, 1H), 7.88 (d, J=9.0 Hz, 1H), 7.78 (dd, J=9.5 and 1.5 Hz, 1H), 7.65 (d, J=8.7 Hz, 2H), 7.07-7.01 (m, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.57 (s, 3H). MS: m/z 440.1, 442.1 [M+H⁺].

Example 66

3-(2-Methoxy-4-methylphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.03 (m, 1H), 7.90 (dd, J=9.5 and 1.2 Hz, 1H), 7.75 (dd, J=9.6 and 1.5 Hz, 1H), 7.64 (d, J=8.7 Hz, 2H), 7.49 (d, J=7.5 Hz, 1H), 7.15 (s, 1H), 7.05-6.99 (m, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 2.46 (s, 3H). MS: m/z 346.2 [M+H⁺].

Example 67

6-(4-Methoxyphenyl)-3-(2-trifluoromethoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.27 (s, 1H), 7.99-7.92 (m, 2H), 7.84-7.78 (m, 2H), 7.70-7.65 (m, 4H), 7.05 (d, J=8.7 Hz, 2H), 3.80 (s, 3H). MS: m/z 386.1 [M+H⁺].

Example 68

6-(4-Methoxyphenyl)-3-phenyl-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.52 (s, 1H), 8.01-7.92 (m, 3H), 7.77-7.58 (m, 6H), 7.06 (d, J=8.7 Hz, 2H), 3.81 (s, 3H). MS: m/z 302.2 [M+H⁺].

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Example 69

6-(4-Methoxyphenyl)-3-(2,4,5-trimethoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.01 (m, 1H), 7.90 (dd, J=9.6 and 0.9 Hz, 1H), 7.74 (dd, J=9.6 and 1.5 Hz, 1H), 7.64 (d, J=8.7 Hz, 2H), 7.16 (s, 1H), 7.05 (d, J=9.0 Hz, 2H), 6.95 (s, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H). MS: m/z 392.2 [M+H⁺].

Example 70

3-(2-Methoxy-4-nitrophenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.30 (m, 1H), 8.06-8.03 (m, 2H), 7.98-7.91 (m, 2H), 7.84-7.81 (dd, J=9.3 and 1.5 Hz, 1H), 7.69 (d, J=8.7 Hz, 2H), 7.05 (d, J=9.0 Hz, 2H), 4.00 (s, 3H), 3.80 (s, 3H). MS: m/z 377.1 [M+H⁺].

Example 71

3-(2,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.02 (m, 1H), 7.89 (dd, J=9.6 and 0.9 Hz, 1H), 7.73 (dd, J=9.6 and 1.8 Hz, 1H), 7.64 (d, J=8.7 Hz, 2H), 7.53 (d, J=8.4 Hz, 1H), 7.04 (d, J=8.7 Hz, 2H), 6.84 (d, J=2.4 Hz, 1H), 6.77 (dd, J=8.7 and 2.4 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H). MS: m/z 362.2 [M+H⁺].

Example 72

6-(4-Methoxyphenyl)-3-(2,3,4-trimethoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.11 (s, 1H), 7.90 (d, J=9.3 Hz, 1H), 7.75 (dd, J=9.6 and 1.5 Hz, 1H), 7.64 (d, J=9.0 Hz, 2H), 7.34 (d, J=8.7 Hz, 1H), 7.02-7.06 (m, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 3.62 (s, 3H). MS: m/z 363.0 [M+H⁺].

Example 73

3-(2,3-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.08 (m, 1H), 7.92 (dd, J=9.6 and 0.9 Hz, 1H), 7.76 (dd, J=9.6 and 1.8 Hz, 1H), 7.62 (d, J=9.0 Hz, 2H), 7.37-7.27 (m, 2H), 7.21 (dd, J=7.2 and 2.1 Hz, 1H), 7.04 (d, J=9.0 Hz, 2H), 3.91 (s, 3H), 3.79 (s, 3H), 3.53 (s, 3H). MS: m/z 392.2 [M+H⁺].

Example 74

3-(2-Ethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.12 (s, 1H), 7.91 (d, J=9.6 Hz, 1H), 7.78 (d, J=9.6 Hz, 1H), 7.68-7.59 (m, 4H), 7.28 (d, J=8.4 Hz,

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1H), 7.17 (t, J=7.5 Hz, 1H), 7.05 (d, J=8.7 Hz, 2H), 4.15 (q, J=6.9 Hz, 2H), 3.79 (s, 3H), 1.05 (t, J=6.9 Hz, 3H). MS: m/z 346.2 [M+H⁺].

Example 75

6-(4-Methoxyphenyl)-3-(2-methoxy-5-sulfamoylphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.22 (m, 1H), 8.07-8.04 (m, 2H), 7.95 (dd, J=9.6 and 0.9 Hz, 1H), 7.80 (dd, J=9.6 and 1.8 Hz, 1H), 7.68 (d, J=8.7 Hz, 2H), 7.48 (d, J=9.3 Hz, 1H), 7.42 (s, 2H), 7.04 (d, J=9.0 Hz, 2H), 3.94 (s, 3H), 3.80 (s, 3H). MS: m/z 411.1 [M+H⁺].

Example 76

3-(2-Methoxy-5-methylphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.02 (s, 1H), 7.91 (d, J=9.6 Hz, 1H), 7.76 (d, J=9.6 Hz, 1H), 7.64 (d, J=9.0 Hz, 2H), 7.45-7.43 (m, 2H), 7.21 (d, J=8.4 Hz, 1H), 7.04 (d, J=8.7 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 2.35 (s, 3H). MS: m/z 346.2 [M+H⁺].

Example 77

3-(3-Methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.54 (s, 1H), 7.96 (d, J=9.3 Hz, 1H), 7.80 (d, J=9.6 Hz, 1H), 7.70 (d, J=8.7 Hz, 2H), 7.55-7.50 (m, 3H), 7.10-7.19 (m, 1H), 7.07 (d, J=8.7 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 3H). MS: m/z 332.2 [M+H⁺].

Example 78

6-(4-Methoxyphenyl)-3-(2-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.05 (m, 1H), 7.94 (dd, J=9.6 and 0.9 Hz, 1H), 7.76 (dd, J=9.6 and 1.5 Hz, 1H), 7.64-7.60 (m, 3H), 7.54-7.51 (m, 2H), 7.44 (m, 1H), 7.03 (d, J=8.7 Hz, 2H), 3.79 (s, 3H), 2.24 (s, 3H). MS: m/z 316.2 [M+H⁺].

Example 79

6-(4-Methoxyphenyl)-3-(2-methylaminophenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.09 (s, 1H), 7.93 (d, J=9.6 Hz, 1H), 7.75 (dd, J=9.6 and 1.5 Hz, 1H), 7.62 (d, J=9.0 Hz, 2H), 7.52 (dd, J=7.5 and 1.5 Hz, 1H), 7.42 (t, J=7.8 Hz, 1H), 7.05 (d, J=9.0 Hz, 2H), 6.83-6.77 (m, 2H), 5.92 (m, 1H), 3.80 (s, 3H), 2.75 (d, J=4.8 Hz, 3H). MS: m/z 331.2 [M+H⁺].

Example 80

3-(2-Dimethylaminophenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 7.94-7.91 (m, 2H), 7.77 (dd, J=9.6 and 1.5 Hz, 1H), 7.61-7.53 (m, 4H), 7.28 (d, J=7.8 Hz, 1H), 7.15 (t, J=7.5 Hz, 1H), 7.04 (d, J=8.7 Hz, 2H), 3.79 (s, 3H), 2.43 (s, 6H). MS: m/z 345.5 [M+H⁺].

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Example 81

6-(3-Amino-4-methoxyphenyl)-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride

A solution of 6-(3-amino-4-methoxyphenyl)-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (50 mg, 0.131 mmol) in HCl/ethyl acetate (2M, 20 mL) was stirred at room temperature for 0.5 h. It was concentrated under reduced pressure to give the title compound (56 mg, 94% yield) as gray solids. ¹H NMR (DMSO-d₆): 8.32 (s, 1H), 8.10 (d, J=9.6 Hz, 1H), 7.95 (dd, J=9.6 and 1.5 Hz, 1H), 7.79 (d, J=2.1 Hz, 1H), 7.73 (dd, J=8.7 and 2.1 Hz, 1H), 7.66 (d, J=8.1 Hz, 1H), 7.45 (d, J=1.5 Hz, 1H), 7.32-7.27 (m, 2H), 3.94 (s, 3H), 3.93 (s, 3H). MS: m/z 381.2 [M+H⁺].

The following salts were prepared from the corresponding free base and HCl/ethyl acetate using a procedure similar to those described for the synthesis of Example 81.

Example 82

6-(3-Amino-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride

¹H NMR (DMSO-d₆): 8.11 (s, 1H), 8.04 (d, J=9.3 Hz, 1H), 7.89 (dd, J=9.6 and 1.5 Hz, 1H), 7.58-7.50 (m, 3H), 7.23 (d, J=8.4 Hz, 1H), 7.18 (s, 1H), 7.03 (d, J=7.8 Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 2.46 (s, 3H). MS: m/z 361.2 [M+H⁺].

Example 83

3-(4-Chloro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride

¹H NMR (DMSO-d₆): 8.23 (m, 1H), 7.96 (d, J=9.6 Hz, 1H), 7.86 (dd, J=9.6 and 1.5 Hz, 1H), 7.70-7.62 (m, 3H), 7.41 (d, J=1.8 Hz, 1H), 7.26 (dd, J=8.1 and 1.8 Hz, 1H), 7.05 (d, J=8.7 Hz, 2H), 3.88 (s, 3H), 3.80 (s, 3H). MS: m/z 366.2 [M+H⁺].

Example 84

3-(2-Methoxy-4-methylphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride

¹H NMR (DMSO-d₆): 8.21 (s, 1H), 8.05-7.97 (m, 2H), 7.71-7.66 (m, 2H), 7.52 (d, J=7.8 Hz, 1H), 7.18 (s, 1H), 7.07-7.02 (m, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 2.47 (s, 3H). MS: m/z 346.2 [M+H⁺].

Example 85

3-(2-Chloropyridin-3-yl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

The title compound was prepared from 2-hydrazinyl-5-(4-methoxyphenyl)pyridine and 2-methoxynicotinic acid using procedures similar to those described for the synthesis of Examples 57c-d, and was isolated as gray solids (230 mg, 68.2% yield). ¹H NMR (DMSO-d₆): 8.71 (dd, J=4.8 and 1.8 Hz, 1H), 8.44 (s, 1H), 8.26 (dd, J=7.7 and 1.8 Hz, 1H), 7.99 (d, J=9.6 Hz, 1H), 7.84 (m, 1H), 7.72-7.68 (m, 3H), 7.04 (d, J=8.7 Hz, 2H), 3.80 (s, 3H). MS: m/z 337.1 [M+H⁺].

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Example 86

6-(4-Methoxyphenyl)-3-(2-methoxypyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridine

A mixture of 3-(2-chloropyridin-3-yl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (178 mg, 0.53 mmol) and sodium methoxide (518 mg, 9.6 mmol) in methanol (60 mL) was heated to reflux for 16 h under Argon. The reaction mixture was cooled to room temperature and concentrated. The residue was mixed with DCM (60 mL) and water (60 mL), and it was separated and the organic layer was washed with brine (50 mL×2) and concentrated. The residue was stirred at room temperature for 0.5 h in petroleum ether (35 mL) and ethyl acetate (5 mL) and filtered. The solids were dried in vacuo to give the title compound (150 mg, 84.0% yield). ¹H NMR (DMSO-d₆): 8.47 (dd, J=4.8 and 1.8 Hz, 1H), 8.32 (m, 1H), 8.10 (dd, J=7.2 and 1.8 Hz, 1H), 7.94 (dd, J=9.6 and 0.9 Hz, 1H), 7.79 (dd, J=9.6 and 1.5 Hz, 1H), 7.69 (d, J=8.7 Hz, 2H), 7.27 (dd, J=7.5 and 5.1 Hz, 1H), 7.05 (d, J=9.0 Hz, 2H), 3.95 (s, 3H), 3.80 (s, 3H). MS: m/z 333.2 [M+H⁺].

Example 87

3-(4-Amino-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride

A mixture of 3-(2-methoxy-4-nitrophenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (50 mg, 0.13 mmol) and SnCl₂ (120 mg, 0.65 mmol) in ethyl acetate (25 mL) was heated to reflux for 6 h under Argon. The reaction mixture was cooled to room temperature and basified to pH=10 with saturated aqueous Na₂CO₃. The biphasic solution was separated and the aqueous layer was extracted with ethyl acetate (40 mL). The combined organic layers were washed with brine and concentrated. The residue was purified by flash column chromatography (petroleum ether:ethyl acetate=2:1 to 0:1) to give crude product as yellow oil. The oil was stirred in a solution of HCl in ethyl acetate (2M, 20 mL) at room temperature, and then was mixed with water (30 mL). The aqueous phase was washed with ethyl acetate (30 mL), basified with saturated aqueous Na₂CO₃ to pH>10 and extracted with ethyl acetate (30 mL). The organic phase was stirred with a solution of HCl in ethyl acetate (2M, 10 mL) at room temperature for 2 h and concentrated in vacuo to give the title compound as yellow solids (16 mg, 30% yield). ¹H NMR (DMSO-d₆): 8.32 (s, 1H), 8.19 (dd, J=9.6 and 1.2 Hz, 1H), 8.09 (d, J=9.6 Hz, 1H), 7.72 (d, J=8.7 Hz, 2H), 7.36 (d, J=8.4 Hz, 1H), 7.08 (d, J=8.7 Hz, 2H), 6.61 (d, J=1.5 Hz, 1H), 6.52 (dd, J=8.4 and 1.5 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H). MS: m/z 347.1 [M+H⁺].

The following compounds were prepared from 6-bromo-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine or 6-chloro-3-(4-methyl-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine and the corresponding phenylboronic acid using a procedure similar to those described for the synthesis of Example 1d.

Example 88

3-(4-Chloro-2-methoxyphenyl)-6-(4-methylaminophenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 8.02 (s, 1H), 7.86 (d, J=8.7 Hz, 1H), 7.73 (d, J=8.7 Hz, 1H), 7.61 (d, J=7.8 Hz, 1H), 7.48-7.40 (m,

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3H), 7.25 (d, J=6.9 Hz, 1H), 6.61 (d, J=6.9 Hz, 2H), 5.96 (s, 1H), 3.87 (s, 3H), 2.70 (s, 3H). MS: m/z 365.2 [M+H⁺].

Example 89

3-(4-Chloro-2-methoxyphenyl)-6-(3-hydroxy-4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 9.21 (s, 1H), 8.06 (m, 1H), 7.90 (dd, J=9.6 and 0.9 Hz, 1H), 7.71 (dd, J=9.6 and 1.5 Hz, 1H), 7.63 (d, J=8.1 Hz, 1H), 7.42 (s, 1H), 7.26 (d, J=8.1 Hz, 1H), 7.14-7.09 (m, 2H), 7.01 (d, J=8.1 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H). MS: m/z 382.1 [M+H⁺].

Example 90

6-(3-Amino-4-methylphenyl)-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 7.99 (m, 1H), 7.91 (dd, J=9.3 and 0.6 Hz, 1H), 7.70-7.62 (m, 2H), 7.42 (s, 1H), 7.27 (dd, J=8.1 and 2.1 Hz, 1H), 7.02 (d, J=7.8 Hz, 1H), 6.88 (s, 1H), 6.80 (dd, J=7.8 and 1.8 Hz, 1H), 5.01 (s, 2H), 3.89 (s, 3H), 2.08 (s, 3H). MS: m/z 365.1 [M+H⁺].

Example 91

6-(3-Amino-4-methylphenyl)-3-(4-methyl-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (DMSO-d₆): 7.91-7.87 (m, 2H), 7.67 (d, J=7.8 Hz, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.16 (s, 1H), 7.02 (d, J=7.8 Hz, 2H), 6.85 (s, 1H), 6.81-6.78 (m, 1H), 5.02 (s, 2H), 3.83 (s, 3H), 2.45 (s, 3H), 2.07 (s, 3H). MS: m/z 345.2 [M+H⁺].

Example 92

6-(4-Methylaminophenyl)-3-(4-methyl-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine

¹H NMR (CD₃OD): 7.88 (m, 1H), 7.79 (m, 2H), 7.51 (d, J=7.8 Hz, 1H), 7.39 (d, J=6.6 Hz, 2H), 7.13 (s, 1H), 7.03 (d, J=7.8 Hz, 1H), 6.69 (d, J=6.6 Hz, 2H), 3.87 (s, 3H), 2.80 (s, 3H), 2.50 (s, 3H). MS: m/z 345.2 [M+H⁺].

Example 93

Identification of 3-(2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine and analogs as inhibitors of cell proliferation that were evaluated with standard MTT cancer cell cytotoxicity assay (IC₅₀)

Human lung cancer cell line A549, breast cancer cell line T47D, liver cancer cell lines HepG2 and SMMC7721 as well as a mouse melanoma cell line B16F10 were used in the study. The cells were cultured in corresponding growth media recommended by American Type Culture Collection (ATCC) with the supplementation of penicillin G (100 U/ml)/streptomycin (100 lg/ml), and 10% fetal bovine serum (Hangzhou

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Sijiqing Biological Engineering Materials, Co., Ltd. China) at 37° C. in a humidified atmosphere containing 5% CO₂. Cells at about 80% confluency were harvested by trypsinization. Cells were centrifuged, re-suspended in fresh growth media and counted. Corresponding numbers of cells were seeded to 96-well cell culture plates (HepG2 cell, T-47D and A549 cells at 3000 cells/well, SMMC-7721 cells at 5000 cells/well and B16F10 cells at 2000 cells/well) in a total volume of 100 μ l. Cells were incubated in CO₂ incubator over night to allow the cells to attach. In next day, 100 μ l of medium containing testing (from 10 μ M to 1 nM) or reference compounds was added to each well of the cells. Media without compound were used as 100% control. Cells were treated with each concentration of compounds in triplicates to ensure data accuracy. Cells were incubated with compounds in CO₂ incubator for an additional 48-72 h at 37° C. After incubation, cells were removed from the CO₂ incubator and 201 of 5 mg/ml MTT (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazoliumbromide, Sigma) solution in PBS was added to each well. Cells were returned to CO₂ incubator and incubated for additional 4 h. After the incubation, media were removed by aspiration and 100 μ l DMSO was added to each well. Plates were sealed with aluminum foil and shaken mildly on an orbital shaker for 10 min at room temperature. The absorption was measured at 550 nm with a plate reader (Varioskan Flash, Thermo Fisher Scientific) with 660 nm reading used as background control. The relative absorbance readings were calculated by subtracting readings at 660 nm from that at 550 nm. The relative absorbance was plotted again the concentrations of the testing compounds and the plots were fitted with a one-site lg(IC₅₀) equation using Prism 5 software (GraphPad Software, Inc). The equation used in the curve fitting is as follows: relative absorbance reading=background reading+(maximal reading-brackground reading)/(1+10^{^(compound concentration-log IC₅₀)}). The background reading used in the calculation was obtained with 100% cell death using a reference anticancer drug, whereas the maximal reading was obtained in the well with no added compound. The IC₅₀ value calculated from the equation represents the cytotoxic potency of a particular compound.

The IC₅₀ values (nM) are summarized in Table I.

TABLE I

Example #	IC ₅₀ in cancer cells			
	IC ₅₀ (nM)			
	A549	HepG2	SMMC7721	T47D
1	35	28	13	37
2	252	189	79	184
3	>10000	>10000	>10000	>10000
4	276	246	80	326
5	11	32	11	40
6	1060	1163	535	697
7	217	136	59	158
8	91	55	24	103
9	>10000	>10000	>10000	>10000
10	>10000	382	618	1370
11	>10000	5288	2906	>10000
12	7180	2951	>10000	>10000
13	2351	1285	1007	660
14	1268	797	110	1437
15	1031	1729	1107	2013
16	160	107	33	152

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TABLE I-continued

IC ₅₀ in cancer cells				
IC ₅₀ (nM)				
Example #	A549	HepG2	SMMC7721	T47D
17	29	48	14	65
18	>10000	>10000	>10000	>10000
19	221	157	68	169
20	13	11	>10000	18
21	>10000	4250	>10000	>10000
22	192	224	51	147
23	215	180	76	134
24	>10000	>10000	>10000	>10000
25	725	724	114	415
26	33	23	12	52
27	9630	2642	2251	4259
28	886	448	178	495
29	>10000	>10000	>10000	>10000
30	>10000	2370	1756	5156
31	241	474	492	765
32	157	83	39	148
33	630	772	164	804
34	>10000	>10000	>10000	>10000
35	20	19	9.9	68
36	74	78	29	315
37	7125	3559	3340	9341
38	49	80	27	74
39	2998	3253	5440	>10000
40	2659	2462	72	896
41	212	155	117	129
42	489	312	230	279
43	>10000	1636	2204	2246
44	54	29	20	48
45	2934	1248	829	678
46	9.4	9.9	5.7	9.7
47	1052	717	365	189
48	26	31	11	18
49	4.9	3.3	4.6	4.5
50	1.7	1.4	1.3	1.1
51	4.0	1.1	>10000	1.1
52	2.6	2.3	1.8	2.0
53	7.4	5.7	8.3	6.7
54	428	134	94	151
55	122	88	58	260
56	>10000	706	1817	1478
57	3.4	3.4	6.7	4.1
58	59	35	17	54
59	12	7.1	3.8	6.6
60	91	41	18	68
61	2556	949	258	2924
62	142	77	42	156
63	174	236	36	149
64	641	568	150	341
65	2459	944	199	569
66	12	15	3.7	19
67	471	910	105	328
68	7748	5031	755	2944
69	833	915	307	834
70	6.7	22	9.9	13
71	16	15	8.7	22
72	>10000	>10000	4138	8157
73	>10000	2350	3209	5325
74	146	141	38	151
75	>10000	>10000	>10000	>10000
76	533	283	104	633
77	4878	2211	962	1954
78	610	264	109	129
79	167	122	69	73
80	118	81	35	62
85	>10000	3874	1894	4342
86	41	58	32	40
87	711	356	175	308
88	4.4	6.0	1.8	3.6
89	1.6	1.4	>10000	0.84
90	7.1	5.4	2.3	5.5
91	42	39	13	31
92	11	23	23	8.8

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The IC₅₀ values (nM) in B16F10 cells are summarized in Table II.

TABLE II

5	IC ₅₀ values (nM) in B16F10 cells							
	Example #							
	1	2	3	5	6	7	11	
10	IC ₅₀ (nM)	36	152	>10000	37	591	220	4999
	Example #							
	20	24	26	27	34	35	38	
15	IC ₅₀ (nM)	18	>10000	23	3825	>10000	16	129
	Example #							
	39	40	46	49	50	51	52	
20	IC ₅₀ (nM)	>10000	>10000	3.7	4.9	1.6	2.1	2.1
	Example #							
	53	57	59	60	66	70	88	
25	IC ₅₀ (nM)	6.2	1.6	6.1	37	3.4	4.4	5.1
	Example #							
	89	90	91	92				
30	IC ₅₀ (nM)	1.1	4.6	23	7.7			

Thus, 3-(2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine (Example 1) and analogs are identified as potent inhibitors of cell proliferation in several solid tumor cell lines.

Example 94

Identification of 3-(2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4] triazolo[4,3-a]pyridine and analogs as inducers of apoptosis in solid tumor cells

Human breast cancer cell line T-47D and lung cancer cell line A549, growing in DMEM/F12+10% FBS media were seeded to a density of 20000 cells/well in 96-well cell culture plate and grew overnight (18-24 h) in CO₂ cell culture incubator at 37° C. Next day the medium were removed by aspiration and 1801 fresh growth media was added to each well followed by 201 of growth media containing 10× concentration of reference or testing compounds with 10% DMSO. Twenty four hours later, cell culture plates were centrifuged at 1000 g for 5 min and the supernatant was removed by emptying contents into a reservoir. Fifty µl of Lysis Buffer (10 mM Tris, pH7.5, 0.1M NaCl, 1 Mm EDTA, 0.01% Triton X-100) was added to each well and the plates were incubated with gentle agitation on an orbital shaker at 4° C. for 30 min. The plates were then centrifuged at 1000 g for 10 min at 4° C. and 20 µl of the supernatant was transferred from each well to a corresponding well in a black 384-well. Twenty µl of caspase-3 assay buffer (20 mM PIPES, pH7.4, 4 Mm EDTA and 0.2% CHAPS) containing 20 µM fluorogenic caspase-3 substrate ((Ac-DEVD)₂-R110, AnaSpec Cat #60304-5) was added to each well. The samples were mixed by agitation and incubated at 37° C. for 3 h. The fluorescent intensity of each well was read on a fluorescent plate reader (Varioskan Flash, Thermo Fisher Scientific) with excitation wavelength at 496 nm and emission wavelength at 520 nm. The activity of com-

pounds on caspase-3 activation was determined by plotting the relative fluorescent unit (RFU) against the testing concentrations of the compounds. The EC₅₀ values were determined by fitting the above responding curves into Prism sigmoidal dose-response equation (GraphPad Software, Inc).

The potency (EC₅₀) of compounds to induce caspase-3 activation is summarized in Table III.

TABLE III

EC ₅₀ values in T47D and A549 cells		
Example #	EC ₅₀ (nM)	
	T47D	A-549
1	55	83
5	76	93
17	86	ND
20	16	ND
26	240	32
35	228	25
46	23	ND
48	74	ND
49	9.3	ND
50	3.5	ND
51	2.8	ND
52	5.4	ND
53	9.1	ND
57	20	5.0
59	25	ND
66	62	11
70	22	ND
71	117	ND
89	2.3	ND

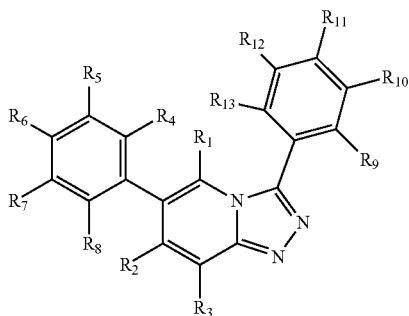
ND, not determined

Thus, 3-(2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine (Example 1) and analogs are identified as potent apoptosis inducers in human breast cancer cell line T-47D and lung cancer cell line A549.

Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

What is claimed is:

1. A compound of Formula II:



or a pharmaceutically acceptable salt thereof, wherein:

R₁-R₃ independently are hydrogen or C₁₋₆ alkyl;

R₄-R₁₃ independently are hydrogen, halo, C₁₋₆ alkoxy, C₁₋₁₀ alkyl, halo C₁₋₆ alkyl, nitro, hydroxy, primary amino (—NH₂), secondary amino (—NHR), tertiary

amino (—NRR), or aminosulfonyl; wherein each R is independently C₁₋₆ alkyl; with the proviso that at least one R₄-R₁₃ is independently C₁₋₆ alkoxy; or

R₄ and R₅, or R₅ and R₆, or R₆ and R₇, or R₇ and R₈, taken together with the atoms to which they are attached to form —OCH₂O— or —OCH₂CH₂O—.

2. The compound of claim 1, wherein said compound is selected from the group consisting of:

3-(2-Methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3-(2-Methoxyphenyl)-6-(3-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3,6-Bis(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(2-Fluoro-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(4-Methoxy-3-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(4-Isopropoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(4-Ethylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(4-Methoxy-2-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Hydroxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(4-Hydroxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(Benzo[d][1,3]dioxol-5-yl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(4-Ethoxy-3-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(4-Dimethylaminophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Chloro-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Hydroxy-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3-(2-Methoxyphenyl)-6-(4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3-(2-Methoxyphenyl)-6-(3-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3-(2-Methoxyphenyl)-6-phenyl-[1,2,4]triazolo[4,3-a]pyridine;

6-(2,4-Dimethylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Chloro-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3-(2-Methoxyphenyl)-6-(4-trifluoromethylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Methoxy-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3-(2-Methoxyphenyl)-6-(3,4,5-trimethoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3,5-Dimethyl-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3,4-Dimethoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3,4-Dimethylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Fluoro-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(4-Hexyloxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Fluoro-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(2,4-Dimethoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

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6-(4-Ethoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(4-Hydroxy-3-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(4-Amino-3-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(3-Amino-4-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(3-Aminophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride;
 6-(3-Amino-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride;
 6-(4-Aminophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride;
 6-(4-Methylaminophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride;
 3-(4-Chloro-2-methoxyphenyl)-6-(3-fluoro-4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(3-Amino-4-methoxyphenyl)-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(3-Hydroxy-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(3-Amino-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(3-Fluoro-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(2-Methoxyphenyl)-6-(4-methoxyphenyl)-7-methyl-[1,2,4]triazolo[4,3-a]pyridine;
 3-(2-Methoxyphenyl)-6-(4-methoxyphenyl)-8-methyl-[1,2,4]triazolo[4,3-a]pyridine;
 6-(4-Hydroxy-3-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(4-Chloro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(4-Fluoro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(4-Bromo-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(2-Methoxy-4-trifluoromethylphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(2,6-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(2,5-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(6-Fluoro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3,6-Bis(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(3-Bromo-2,6-dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(2-Methoxy-4-methylphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-phenyl-[1,2,4]triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-(2,4,5-trimethoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(2,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-(2,3,4-trimethoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(2,3-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(2-Ethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-(2-methoxy-5-sulfamoylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

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3-(2-Methoxy-5-methylphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(3-Methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(4-Methoxyphenyl)-3-(2-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(4-methoxyphenyl)-3-(2-methylaminophenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(2-dimethylaminophenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(3-Amino-4-methoxyphenyl)-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride;
 6-(3-Amino-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride;
 3-(4-Chloro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride;
 3-(2-Methoxy-4-methylphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride;
 3-(4-Amino-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride;
 3-(4-Chloro-2-methoxyphenyl)-6-(4-methylaminophenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 3-(4-Chloro-2-methoxyphenyl)-6-(3-hydroxy-4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(3-Amino-4-methylphenyl)-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 6-(3-Amino-4-methylphenyl)-3-(4-methyl-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine; and
 6-(4-Methylaminophenyl)-3-(4-methyl-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;
 or a pharmaceutically acceptable salt thereof.
 3. A method of treating a disorder responsive to the inhibition of uncontrolled cell proliferation in a mammal suffering therefrom, comprising administering to the mammal in need of such treatment an effective amount of a compound of claim 1, wherein said disorder is cancer.
 4. The method according to claim 3, wherein said cancer is Hodgkin's disease, non-Hodgkin's lymphomas, acute or chronic lymphocytic leukemia, multiple myeloma, neuroblastoma, breast carcinoma, ovarian carcinoma, lung carcinoma, Wilms' tumor, cervical carcinoma, testicular carcinoma, soft-tissue sarcoma, chronic lymphocytic leukemia, primary macroglobulinemia, bladder carcinoma, chronic granulocytic leukemia, primary brain carcinoma, malignant melanoma, small-cell lung carcinoma, stomach carcinoma, colon carcinoma, malignant pancreatic insulinoma, malignant carcinoid carcinoma, malignant melanoma, choriocarcinoma, mycosis fungoides, head or neck carcinoma, osteogenic sarcoma, pancreatic carcinoma, acute granulocytic leukemia, hairy cell leukemia, neuroblastoma, rhabdomyosarcoma, Kaposi's sarcoma, genitourinary carcinoma, thyroid carcinoma, esophageal carcinoma, malignant hypercalcemia, cervical hyperplasia, renal cell carcinoma, endometrial carcinoma, polycythemia vera, essential thrombocythosis, adrenal cortex carcinoma, skin cancer, or pro static carcinoma.
 5. The method of claim 3, wherein said cancer is drug resistant cancer.
 6. The method of claim 3, further comprising administering at least one known anticancer agent, or a pharmaceutically acceptable salt of said agent.
 7. The method according to claim 3, wherein said compound is administered together with at least one compound selected from the group consisting of busulfan, cis-platin, mitomycin C, carboplatin, colchicine, vinblastine, paclitaxel, docetaxel, camptothecin, topotecan, doxorubicin, etoposide, 5-azacytidine, 5-fluorouracil, methotrexate, 5-fluoro-2'-deoxy-uridine, ara-C, hydroxyurea, thioguanine, melphalan,

chlorambucil, cyclophosphamide, ifosfamide, vincristine, mitoguazone, epirubicin, aclarubicin, bleomycin, mitoxantrone, elliptinium, fludarabine, octreotide, retinoic acid, tamoxifen, campath, Herceptin®, Rituxan®, arsenic trioxide, gemcitabine, letrozole, fulvestrant, bendamustine, pralatrexate, pemetrexed, nelarabine, temozolomide, zoledronic acid, irinotecan, ixabepilone, cabazitaxel, vinorelbine, Panitumumab, Ofatumumab, Avastin, imatinib, gefitinib, erlotinib, lapatinib, sorafenib, sunitinib, nilotinib, dasatinib, pazopanib, bortezomib, vorinostat, romidepsin, temsirolimus, everolimus, thalidomide, lenalidomide, and alanosine.

8. The method of claim 3, further comprising treating said mammal with radiation-therapy.

9. The method of claim 3, wherein said compound is administered after surgical treatment of said mammal for said cancer.

10. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, further comprising at least one known anticancer agent, or a pharmaceutically acceptable salt of said agent.

12. The pharmaceutical composition of claim 10, further comprising at least one compound selected from the group consisting of busulfan, cis-platin, mitomycin C, carboplatin, colchicine, vinblastine, paclitaxel, docetaxel, camptothecin, topotecan, doxorubicin, etoposide, 5-azacytidine, 5-fluorouracil, methotrexate, 5-fluoro-2'-deoxy-uridine, ara-C, hydroxyurea, thioguanine, melphalan, chlorambucil, cyclophosphamide, ifosfamide, vincristine, mitoguazone, epirubicin, aclarubicin, bleomycin, mitoxantrone, elliptinium, fludarabine, octreotide, retinoic acid, tamoxifen, campath, Herceptin®, Rituxan®, arsenic trioxide, gemcitabine, letrozole, fulvestrant, bendamustine, pralatrexate, pemetrexed, nelarabine, temozolomide, zoledronic acid, irinotecan, ixabepilone, cabazitaxel, vinorelbine, Panitumumab, Ofatumumab, Avastin, imatinib, gefitinib, erlotinib, lapatinib, sorafenib, sunitinib, nilotinib, dasatinib, pazopanib, bortezomib, vorinostat, romidepsin, temsirolimus, everolimus, thalidomide, lenalidomide, and alanosine.

13. The pharmaceutical composition of claim 12, comprising the compound of claim 4 and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim 12, comprising the compound of claim 5 and a pharmaceutically acceptable carrier.

15. The compound of claim 1, wherein R₄-R₈ independently are hydrogen, halo, C₁₋₆ alkoxy, C₁₋₁₀ alkyl, halo C₁₋₆ alkyl, hydroxy, secondary amino (—NHR), tertiary amino (—NRR); or aminosulfonyl; and wherein R₉-R₁₃ independently are hydrogen, halo, C₁₋₆ alkoxy, C₁₋₁₀ alkyl, halo C₁₋₆ alkyl, hydroxy, secondary amino (—NHR), tertiary amino (—NRR), or aminosulfonyl; wherein each R is independently C₁₋₆ alkyl.

16. The compound of claim 1, wherein R₄ and R₅, or R₅ and R₆, or R₆ and R₇, or R₇ and R₈, taken together with the atoms to which they are attached to form —OCH₂O— or —OCH₂CH₂O—.

17. The compound of claim 1, wherein R₄-R₁₃ independently are C₁₋₆ alkoxy, hydroxy, secondary amino (—NHR), tertiary amino (—NRR), or aminosulfonyl; wherein each R is independently C₁₋₆ alkyl.

18. The compound of claim 1, wherein R₄-R₁₃ independently are C₁₋₆ alkoxy.

19. The compound of claim 1, wherein said compound is selected from the group consisting of:

6-(4-Methoxy-3-methylphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(4-Dimethylaminophenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Hydroxy-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Chloro-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Amino-4-methoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine hydrochloride;

3-(4-chloro-2-methoxyphenyl)-6-(3-fluoro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Amino-4-methoxyphenyl)-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Hydroxy-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Amino-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Fluoro-4-methoxyphenyl)-3-(2-methoxy-4-methylphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3-(4-Chloro-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3-(4-Bromo-2-methoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3-(2-Methoxy-4-methylphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3-(2,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3-(4-Chloro-2-methoxyphenyl)-6-(4-methylaminophenyl)-[1,2,4]triazolo[4,3-a]pyridine;

3-(4-Chloro-2-methoxyphenyl)-6-(3-hydroxy-4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Amino-4-methylphenyl)-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

6-(3-Amino-4-methylphenyl)-3-(4-methyl-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine; and

6-(4-Methylaminophenyl)-3-(4-methyl-2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyridine;

or a pharmaceutically acceptable salt thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 9,199,983 B2
APPLICATION NO. : 13/885896
DATED : December 1, 2015
INVENTOR(S) : Cai et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the specification

Column 3

Line 34 please replace “or R7 and R5” with --or R7 and R8--

Column 18

Line 51 please replace “[]trizolo[” with --]triazolo[--

Column 26

Line 43 please replace “prepared form” with --prepared from--

In the claims

Column 41

Line 48 please replace “[4,3- α]” with --[4,3- α]--

Column 42

Line 55 please replace “pro static” with --prostatic--

Column 43

Line 41 please replace “claim 4” with --claim 1--

Column 43

Line 44 please replace “claim 5” with --claim 2--

Signed and Sealed this
Twenty-eighth Day of June, 2016



Michelle K. Lee
Director of the United States Patent and Trademark Office